

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034093 A2(51) International Patent Classification⁷: Not classified(21) International Application Number:
PCT/US2005/033277(22) International Filing Date:
20 September 2005 (20.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/611,718 21 September 2004 (21.09.2004) US
60/696,949 6 July 2005 (06.07.2005) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,

GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

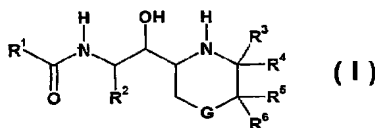
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW. ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW. ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: BACE INHIBITORS



(57) Abstract: The present invention provides BACE inhibitors of Formula (I); methods for their use and preparation, and intermediates useful for their preparation.



*Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL,
PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- without international search report and to be republished upon receipt of that report

BACE INHIBITORS

Alzheimer's disease, characterized by cognitive and behavioral deterioration in its latter stages, has emerged as a significant social and financial concern. With a prevalence approaching 5.5% in the population above the age of 60, the cost for care of Alzheimer's disease patients has been estimated to be in excess of \$100 billion annually. Although cholinesterase inhibitors are somewhat effective in reducing the symptoms of Alzheimer's disease, particularly when the disease is in its early phases, they are not at all effective in slowing or stopping the progression of the disease.

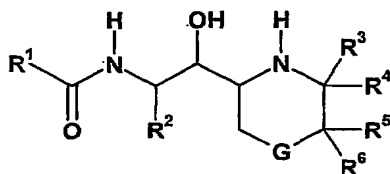
Neurofibrillary tangles and neuritic plaques are generally found in the brain regions associated with memory and cognition of those afflicted with Alzheimer's disease. These plaques are also found in the brains of individuals with Down's syndrome, Hereditary Cerebral Hemorrhage of the Dutch-Type, and other neurodegenerative disorders. The neuritic plaques are comprised primarily of amyloid β ($A\beta$) peptide, a neurotoxic and highly aggregatory peptide segment of amyloid precursor protein (APP). $A\beta$ peptide is formed by the proteolytic cleavage of APP by β -secretase (BACE) followed by at least one subsequent C-terminal cleavage by γ -secretase. As such, inhibition of BACE is an attractive target for the treatment or prevention of Alzheimer's disease as well as other diseases characterized pathologically by amyloid plaques.

BACE is a member of the pepsin sub-family of mammalian aspartyl proteases and, like its substrate APP, is a type I transmembrane protein. BACE has been disclosed in the literature and is referred to also as " β -site APP-cleaving enzyme", "membrane aspartic protease of the pepsin family", "Asp-2", " β -secretase", "membrane-bound aspartic protease" and "Memapsin 2" (See: Ghosh, et al., Current Medicinal Chemistry, 9(11), 1135-1144 (2002)). Two isoforms of BACE have been identified in humans, designated BACE1 and BACE2. It is believed that the BACE1 inhibitory activity is most important to inhibition of amyloid β ($A\beta$) peptide (Roggo, Current Topics in Medicinal Chemistry, 2, 359-370 (2002)). Currently described BACE inhibitors are peptidomimetic transition state analogs, typically containing a hydroxyethyl moiety. Although many of these compounds are potent inhibitors of BACE, their high molecular weights and low membrane permeability make them poor drug candidates. (See: Park and Lee, Journal of the American Chemical Society, 125(52), 16416-16422 (2003)).

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Additional compounds described as BACE inhibitors are disclosed in WO 03/040096, WO 04/024081, WO 04/0039034, and WO 04/043916. Additional BACE inhibitors are necessary to provide treatments for A- β peptide mediated disorders such as Alzheimer's disease. The present invention provides new inhibitors of BACE.

5 The present invention provides compounds of Formula I:



I

where:

10 R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl
15 optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^7$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^7$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

R^2 is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally
20 monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, hydroxy, thiol, benzyloxy, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6
25 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to

three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a second substituent selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is hydrogen; R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl; or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of treating Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention further provides a method of preventing the progression of mild cognitive impairment to Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

5 The present invention also provides a method of inhibiting BACE in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a method for inhibiting β -secretase mediated cleavage of amyloid precursor protein comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

10 The present invention further provides a method for the inhibition of production of A- β peptide comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically acceptable carrier,
15 diluent, or excipient.

Another embodiment of the present invention is a compound of Formula I for use as a pharmaceutical. Furthermore, this invention provides the use of a compound of Formula I for the manufacture of a medicament for the treatment of Alzheimer's disease. This invention also provides the use of a compound of Formula I for the manufacture of a
20 medicament for the prevention of the progression of mild cognitive impairment to Alzheimer's disease. The invention also provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of BACE. The present invention also provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of β -secretase mediated cleavage of amyloid precursor protein. The invention
25 further provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of production of A- β peptide.

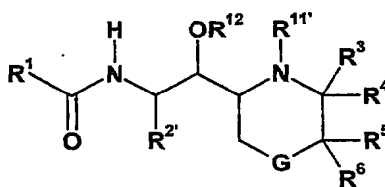
Additionally, this invention provides a pharmaceutical formulation adapted for the treatment of Alzheimer's disease. Furthermore, this invention provides a pharmaceutical formulation adapted for the prevention of the progression of mild cognitive impairment to
30 Alzheimer's disease. This invention also provides a pharmaceutical formulation adapted for the inhibition of BACE.

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Furthermore the present invention provides a pharmaceutical formulation adapted for the inhibition of β -secretase mediated cleavage of amyloid precursor protein. The present invention also provides a pharmaceutical formulation adapted for the treatment of conditions resulting from excessive levels of A- β peptide comprising a compound of

5 Formula I or a pharmaceutically acceptable salt thereof in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents.

This invention also provides intermediates of Formula II:



II

10

where:

R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^7$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^7$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

20

$R^{2'}$ is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally

25

substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a
 5 second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in
 10 the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

15 R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

20 G is O;

R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

25 R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

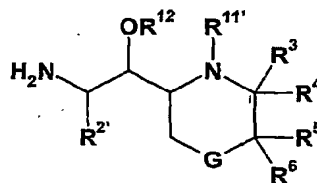
R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆
 30 alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl;

R¹¹ hydrogen or a nitrogen protecting group;

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R^{12} is hydrogen or an oxygen protecting group; or an acid addition salt thereof provided that at least one of $R^{11'}$ and R^{12} is other than hydrogen.

Additionally, the present invention provides intermediates of Formula III:



III

where:

- $R^{2'}$ is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a second substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with

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three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together
5 with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

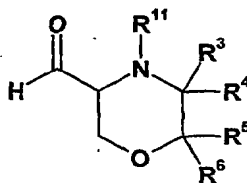
R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-
10 (C₁-C₆ alkyl)silyl; C₁-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl;
or phenyl each optionally substituted with one substituent selected from the group
consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or one or
two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl
15 optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy,
and trifluoromethoxy; or R¹⁰ is adamantyl;

R¹¹ is hydrogen or a nitrogen protecting group;

R¹² is hydrogen or an oxygen protecting group; or an acid addition salt thereof.

The present invention also provides intermediates of Formula IV:



IV

where:

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together
25 with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

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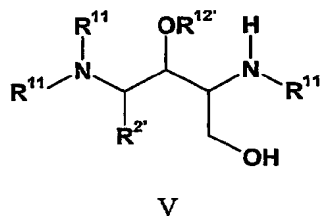
R^9 is hydrogen; C_1 - C_{10} alkyl optionally substituted with 1-6 fluorine atoms or tri-
(C_1 - C_6 alkyl)silyl; C_1 - C_{10} acyl; C_2 - C_6 alkenyl; or $-(CH_2)_{0-4}-R^{10}$;

R^{10} is C_3 - C_8 cycloalkyl; C_3 - C_8 cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl;
or phenyl each optionally substituted with one substituent selected from the group

5 consisting of C_3 - C_8 cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or one or
two substituents independently selected from the group consisting of halo, C_1 - C_6 alkyl
optionally substituted up to three times with fluoro, C_2 - C_6 acyl, C_1 - C_6 alkoxy, hydroxy,
and trifluoromethoxy; or R^{10} is adamantyl;

R^{11} is a nitrogen protecting group; provided that at least one of R^3 , R^4 , R^5 , and R^6
10 are other than hydrogen.

Additionally, the present invention provides intermediates of Formula V:



15 where:

$R^{2'}$ is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally
monosubstituted in the phenyl ring with a substituent selected from the group consisting
of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times
with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6
20 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 -
 C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio
optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6
cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally
substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the
25 phenyl ring with a first substituent selected from the group consisting of halo,
trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three
times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a
second substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl
optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6

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cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

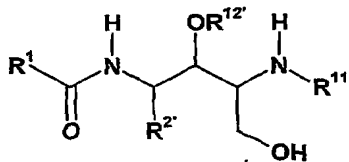
R¹¹ is independently at each instance a nitrogen protecting group;

10 R^{11'} is hydrogen or a nitrogen protecting group;

R¹² is hydrogen or an oxygen protecting group;

R^{12'} is an oxygen protecting group; or an acid addition salt thereof.

Furthermore, the present invention provides intermediates of Formula VI:



15

VI

where:

R¹ is C₁-C₁₀ alkyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl;

C₂-C₈ alkenyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl; C₂-C₈

20 alkynyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl; or C₃-C₈ cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl

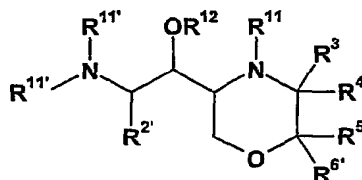
optionally substituted with up to three fluoro atoms, trifluoromethoxy, C₁-C₆ alkoxy, C₃-C₇ cycloalkoxy, oxo, NR⁷R⁸, and C(O)NR⁷R⁷; or R¹ is hydrogen; furyl optionally

25 substituted with C(O)NR⁷R⁷ or up to two times with C₁-C₆ alkyl; thienyl; tetrahydrofuryl; NR⁷R⁸; or C₁-C₆ alkoxy;

R^{2'} is C₁-C₃ alkyl optionally substituted with C₃-C₆ cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times

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- with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;
- R⁷ is selected independently at each occurrence from the group consisting of hydrogen; C₁-C₆ alkyl; and phenyl;
- R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);
- R^{11'} is hydrogen or a nitrogen protecting group;
- R¹² is hydrogen or an oxygen protecting group;
- R^{12'} is an oxygen protecting group; or an acid addition salt thereof.
- Additionally, the present invention provides intermediates of Formula VII:



VII.

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where:

$R^{2'}$ is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a second substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C_1 - C_6 alkyl;

R^3 is hydrogen or C_1 - C_6 alkyl optionally substituted with C_3 - C_8 cycloalkyl or up to three times with fluoro and R^4 is hydrogen or C_1 - C_6 alkyl; or R^3 and R^4 taken together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl ring;

$R^{5'}$ is hydroxy and $R^{6'}$ is hydrogen or $R^{5'}$ and $R^{6'}$ together with the carbon to which they are attached form a carbonyl moiety;

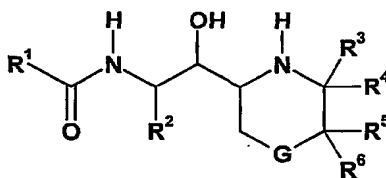
R^{11} is a nitrogen protecting group;

$R^{11'}$ is hydrogen or a nitrogen protecting group;

R^{12} is hydrogen or an oxygen protecting group; or an acid addition salt thereof.

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The present invention further provides a process for the preparation of a compound of Formula I:



I

5 where:

R^1 is hydrogen; C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four
 10 substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^8$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^8$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

R^2 is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, hydroxy, thiol, benzyloxy, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3
 15 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl
 20 disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a second substituent selected from the group consisting of halo, C_1 - C_6 alkyl
 25 optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in

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the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is hydrogen; R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

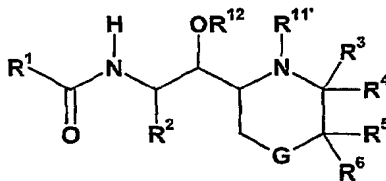
R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl; or a pharmaceutically acceptable salt thereof comprising the steps of:

a) deprotecting a compound of Formula II(a):



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II(a)

where:

R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^8$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^8$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

R^2 is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, hydroxy, thiol, benzyloxy, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a second substituent selected from the group consisting of halo, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with

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three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl;

R¹¹ hydrogen or a nitrogen protecting group;

R¹² is hydrogen or an oxygen protecting group; or an acid addition salt thereof provided that at least one of R¹¹ and R¹² is other than hydrogen; and

b) optionally treating the compound of Formula I with a pharmaceutically acceptable acid to form the corresponding pharmaceutically acceptable salt.

The general chemical terms used in the formulae above have their usual meanings. For example, the term "C₁-C₃ alkyl" includes methyl, ethyl, propyl, and isopropyl, and the terms "C₁-C₈ alkyl" and "C₁-C₁₀ alkyl" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, and hexyl moieties, and the like.

The term "C₃-C₅ cycloalkyl" includes cyclopropyl, cyclobutyl, and cyclopentyl moieties, the term "C₃-C₆ cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and bicyclo[2.1.1]hexyl moieties, likewise, the term "C₃-C₈ cycloalkyl"

includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.1.1]hexyl, cycloheptyl, cyclooctyl, and bicyclo[3.1.1]heptyl moieties.

The term "C₂-C₃ alkenyl" includes ethenyl, prop-1-en-3-yl, prop-1-en-2-yl, and the like. The terms "C₂-C₆ alkenyl", "C₂-C₈ alkenyl" and "C₂-C₁₀ alkenyl" include
5 ethenyl, prop-1-en-3-yl, prop-1-en-2-yl, 2-methylprop-1-en-1-yl, and the like.

The terms "C₂-C₈ alkynyl" and "C₂-C₁₀ alkynyl" include ethynyl, prop-1-yn-3-yl, prop-1-yn-1-yl, 4-methylpent-2-yn-1-yl, and the like.

The term "C₁-C₁₀ acyl" includes formyl, acetyl, propionyl, isobutyryl, and the
like.

10 "Halo" includes fluoro, chloro, bromo, and iodo.

The terms "C₁-C₃ alkoxy" and "C₁-C₆ alkoxy" are a C₁-C₃ alkyl group or a C₁-C₆ alkyl group, respectively, bonded to an oxygen atom and include methoxy, ethoxy, isopropoxy, tert-butoxy, and the like. Similarly, the terms "C₃-C₅ cycloalkoxy" and "C₃-C₈ cycloalkoxy" are a C₃-C₅ cycloalkyl group or a C₃-C₈ cycloalkyl group, respectively,
15 bonded through an oxygen atom and include cyclopropoxy, cyclobutoxy, cyclopentoxy, and the like. Similarly the term "C₁-C₆ alkylthio" is a C₁-C₆ alkyl group bonded to a sulfur atom and include methylthio, ethylthio, isopropylthio, and the like.

The term "C₁-C₁₀ alkyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl" is taken to mean a C₁-C₁₀ alkyl moiety optionally substituted with one C₃-C₈ cycloalkyl, phenyl, or furyl moiety at any available carbon atom in the C₁-C₁₀ alkyl moiety and includes cyclopropylmethyl, 2-cyclohexyleth-1-yl, benzyl, and the like.
20 Similarly, "C₂-C₈ alkenyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl" and "C₂-C₈ alkynyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl" are taken to mean a C₂-C₈ alkenyl or C₂-C₈ alkynyl moiety optionally substituted at any
25 available carbon atom in the C₂-C₈ alkenyl or C₂-C₈ alkynyl moiety. Any of the "C₁-C₁₀ alkyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl", "C₂-C₈ alkenyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl" and "C₂-C₈ alkynyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl" moieties may be further substituted up to three times at any available carbon on the alkyl, alkenyl, or alkynyl
30 chains or in the C₃-C₈ cycloalkyl, phenyl, or furyl rings up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo,

cyano, methyl optionally substituted up to three times with fluoro, trifluoromethoxy, C₁-C₆ alkoxy, C₃-C₇ cycloalkoxy, oxo, NR⁷R⁸, and C(O)NR⁷R⁷.

The term "C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₈ cycloalkyl optionally substituted with C₁-C₃ alkyl" is taken to mean a C₁-C₆ alkoxy moiety optionally substituted either up to three times with fluoro groups at any available carbon atoms in the C₁-C₆ alkoxy moiety or with one C₃-C₈ cycloalkyl moiety at any available carbon atom in the C₁-C₆ alkoxy moiety and said C₃-C₈ cycloalkyl moiety is optionally substituted with a C₁-C₃ alkyl group. Similarly, the terms "C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl" and "C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl" is taken to mean a C₁-C₆ alkylthio moiety or C₁-C₆ alkyl moiety optionally substituted either up to three times with fluoro or with one C₃-C₈ cycloalkyl moiety at any available carbon atoms in the C₁-C₆ alkylthio or C₁-C₆ alkyl moiety and said C₃-C₈ cycloalkyl moiety is optionally substituted with a C₁-C₃ alkyl group.

The term "C₁-C₄ alkyl substituted with C₃-C₈ cycloalkyl" is taken to mean a C₁-C₄ alkyl moiety substituted at any available carbon with a C₃-C₈ cycloalkyl group and includes spiro-fusion of the C₃-C₈ cycloalkyl group to the C₁-C₄ alkyl moiety.

The term "oxo" is taken to mean an oxygen atom double bonded to a carbon atom to form a carbonyl moiety.

The term "C₂-C₆ alkenyloxy" is taken to mean a C₂-C₆ alkenyl moiety bonded through an oxygen atom and include allyloxy, prop-1-en-3-yloxy, and the like.

The term "C₃-C₈ cycloalkanonyl" is taken to mean a C₃-C₈ cycloalkyl moiety substituted with an oxo group and includes cyclohexanone, cyclooctanone and the like.

The term "tri-(C₁-C₆ alkyl)silyl" is taken to mean a silyl group substituted with three substituents independently selected from C₁-C₆ alkyl and includes trimethylsilyl and ethyldimethylsilyl.

The term "nitrogen protecting group" is taken to mean a moiety that is stable to projected reaction conditions and yet may be selectively removed by reagents and reaction conditions compatible with the regenerated amine. Such groups are well known by the skilled artisan and are described in the literature. (See, for example: Greene and

Wuts, Protective Groups in Organic Synthesis, Third Edition, Chapter 7, John Wiley and Sons Inc., (1999)). Nitrogen protecting groups contemplated include:

a) suitable carbamates, such as:

- 5 1) C₁-C₇ alkyl carbamates including methyl, ethyl, tert-butyl, tert-amyl, diisopropylmethyl carbamates, and the like;
- 2) substituted ethyl carbamates, such as 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloro-ethyl, 2-(pyridin-2-yl)ethyl, 2-(pyridin-4-yl)ethyl, 2-methylthioethyl, 2-methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, 2-phosphonioethyl, 1,1-dimethyl-2-cyanoethyl, 2-iodoethyl carbamates, and the like;
- 3) 1-adamantyl carbamate;
- 4) vinyl carbamate;
- 5) allyl carbamate;
- 15 6) 1-isopropylallyl carbamate;
- 7) cinnamyl carbamates, such as cinnamyl carbamate, 4-nitrocinnamyl, and the like;
- 8) 8-quinolinyll carbamate;
- 9) N-hydroxypiperidinyll carbamate;
- 20 10) C₁-C₄ alkyldithio carbamates;
- 11) Benzyl carbamates, such as benzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-halobenzyl, 4-cyanobenzyl, 4-decyloxybenzyl, 2,4-dichlorobenzyl, 3,5-dimethoxybenzyl, 2-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl (2-nitrophenyl)methyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl, 3-chloro-4-(C₂-C₆ acyloxy)benzyl, 4-(dihydroxyboryl)benzyl carbamates, and the like;
- 25 12) 2-(1,3-dithianyl)methyl carbamate;
- 13) aryl carbamates, such as phenyl, nicotinyll, 4-(methylthio)phenyl, 2,4-di(methylthio)phenyl, 3-nitrophenyl carbamates, and the like;
- 30 14) 2-triphenylphosphonioisopropyl carbamate;
- 15) 5-benzisoxazolylmethyl carbamate;
- 16) 2-(trifluoromethyl)-6-chromonylmethyl carbamate;

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- 17) S-benzyl thiocarbamate; and
- 18) C₃-C₈ cycloalkyl carbamates, such as cyclobutyl, cyclopentyl, 1-methylcyclohexyl, cyclopropylmethyl carbamates, and the like;
- b) suitable ureas, such as:
- 5 1) phenothiazinyl-(10)-carbonyl;
- 2) N'-(p-toluenesulfonylaminocarbonyl); and
- 3) N'-phenylaminothiocarbonyl;
- c) suitable formyl and acyl groups, such as:
- 10 1) formyl; and
- 2) acetyl groups, such as acetyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, 4-chlorobutanoyl, phenylacetyl, 3-phenylpropanoyl, N-benzoylphenylalanyl, 2-nitrophenylacetyl, 2-nitrophenoxyacetyl, acetoacetyl, and the like;
- d) suitable aroyl groups, such as:
- 15 1) picolinoyl;
- 2) 3-pyridinylcarbonyl;
- 3) benzoyl;
- 4) 4-phenylbenzoyl;
- 5) 2-nitrobenzoyl; and
- 20 6) 2-nitrocinnamoyl, and the like;
- e) suitable cyclic imide groups, such as:
- 1) N-phthalimide;
- 2) N-dithiasuccinimide;
- 3) N-2,3-diphenylmaleimide; and
- 25 4) N-2,5-dimethylpyrrole, and the like;
- f) allyl;
- g) 3-acetoxypentyl;
- h) suitable benzylic groups, such as benzyl, 2-methylbenzyl, α-methylbenzyl, and the like;
- 30 i) triphenylmethyl; and
- j) suitable imine moieties, such as:
- 1) 1,1-dimethylthiomethyleneimine;

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- 2) benzylidene imine; and
- 3) diphenylmethylenimine, and the like.

The term "oxygen protecting group" is taken to mean a moiety that is stable to projected reaction conditions and yet may be selectively removed by reagents and reaction conditions compatible with the regenerated alcohol. Such groups are well known by the skilled artisan and are described in the literature. (See, for example: Greene and Wuts, Protective Groups in Organic Synthesis, Third Edition, Chapter 7, John Wiley and Sons Inc., (1999)). Oxygen protecting groups contemplated include:

- a) methyl and substituted methyl groups such as methoxymethyl, methylthio-
methyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxy-
benzyloxymethyl, *p*-nitrobenzyloxy-methyl, *o*-nitrobenzyloxymethyl, (4-
methoxyphenoxy)methyl, guaiacolmethyl, *tert*-butoxymethyl, 4-pentenyl-
oxy-methyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroeth-oxymethyl,
bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, 2-quinoliny-
methyl, 1-pyrenylmethyl, diphenylmethyl, triphenylmethyl, and the like;
- b) tetrahydropyranyl and substituted tetrahydropyranyl groups such as 3-
bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-
methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-
methoxytetrahydropyranyl-S,S-dioxide, and the like;
- c) tetrahydrofuranyl and substituted tetrahydrofuranyl groups such as
tetrahydrothiofuranyl and the like;
- d) ethyl and substituted ethyl groups such as 1-ethoxyethyl, 1-(2-chloroethoxy)-
ethyl, 1-[(2-trimethylsilyl)ethoxy]ethyl, 1-methyl-1-methoxy-ethyl, 1-methyl-
1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxy-
ethyl, 2,2,2-trichloroethyl, 1,1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexa-
fluoro-2-phenylisopropyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-
(phenylselenyl)ethyl, *tert*-butyl, and the like;
- e) allyl;
- f) propargyl;
- g) substituted phenyl groups such as *p*-chlorophenyl, *p*-nitrophenyl, 2,4-dinitro-
phenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, and the like;

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- h) benzyl and substituted benzyl groups such as p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2,6-difluorobenzyl, p-acylamino-benzyl, p-azidobenzyl, 4-azido-3-chlorobenzyl, 2-trifluoromethylbenzyl, p-(methylsulfinyl)benzyl, and the like;
- 5 i) silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-tert-butylmethylsilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, tert-butylmethoxyphenyl silyl, tert-butoxydiphenylsilyl, and the like;
- 10 j) formyl and benzoylformyl groups;
- k) acetyl and substituted acetyl groups such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, triphenylmethoxyacetyl, phenoxyacetyl, p-chlorophenoxyacetyl, phenylacetyl, chlorodiphenylacetyl
- 15 and the like;
- l) pivaloyl;
- m) crotonyl;
- n) benzoyl and substituted benzoyl groups such as p-phenylbenzoyl, 2-chlorobenzoyl, 4-bromobenzoyl, 2,4,6-trimethylbenzoyl;
- 20 o) methoxycarbonyl and substituted methoxycarbonyl groups such as methoxymethoxycarbonyl, 9-fluorenylmethoxycarbonyl, and the like;
- p) ethoxycarbonyl and substituted ethoxycarbonyl groups such as 2,2,2-trichloroethoxycarbonyl, 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-dansylethoxycarbonyl, 2-(4-nitrophenyl)-ethoxycarbonyl, 2-(2,4-dinitrophenyl)ethoxycarbonyl, 2-cyano-1-phenyl-ethoxycarbonyl, and the like;
- 25 q) isobutoxycarbonyl;
- r) vinyloxycarbonyl;
- 30 s) allyloxycarbonyl;

- t) substituted phenoxy carbonyl groups such as *p*-nitrophenoxy carbonyl, 2-iodophenoxy carbonyl, 2-chlorophenoxy carbonyl, 4-bromophenoxy carbonyl, 4-nitrophenoxy carbonyl, *o*-(dibromomethyl)phenoxy carbonyl, and the like;
- u) benzyloxy carbonyl and substituted benzyloxy carbonyl groups such as *p*-methoxybenzyloxy carbonyl, 3,4-dimethoxybenzyloxy carbonyl, *o*-nitrobenzyloxy carbonyl, *p*-nitrobenzyloxy carbonyl, and the like; and
- v) sulfonyl groups such as methanesulfonyl, benzylsulfonyl, *p*-toluenesulfonyl, 2-[(4-nitrophenyl)ethyl]sulfonyl, and the like.

The term "inhibition of production of A- β peptide" is taken to mean decreasing of excessive in vivo levels of A- β peptide in a mammal to normal or sub-normal levels.

The term "effective amount of a compound of Formula I" is taken to mean the dose or doses of a compound of Formula I required to inhibit BACE sufficiently to decrease in vivo levels of A- β peptide in a mammal to normal or sub-normal levels.

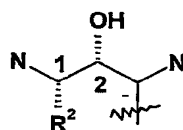
The term "treatment" includes treating one or more disease symptoms present in a patient as well as slowing, arresting, or reversing the progression of the disease.

The term "BACE" includes both BACE1 and BACE2.

Mild cognitive impairment has been defined as a potential prodromal phase of dementia associated with Alzheimer's disease based on clinical presentation and on progression of patients exhibiting mild cognitive impairment to Alzheimer's dementia over time. (Morris, *et al.*, *Arch. Neurol.*, **58**, 397-405 (2001); Petersen, *et al.*, *Arch. Neurol.*, **56**, 303-308 (1999)). The term "prevention of the progression of mild cognitive impairment to Alzheimer's disease" includes slowing, arresting, or reversing the progression of mild cognitive impairment to Alzheimer's disease in a patient.

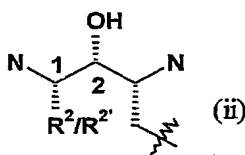
The skilled artisan will understand that compounds of Formulae I – III and V-VII are comprised of a 1-amino-2-hydroxyethyl core that contains two chiral centers. Although the present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates, the 1(S),2(S) diastereomer is preferred for compounds of Formula I as illustrated in Figure (i):

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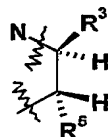
(i).

The preferred diastereomers of compounds of Formulae II, III, and V-VII are those that will result in the 1(S),2(S) diastereomer when the intermediate is converted to a compound of Formula I. The skilled artisan will also appreciate that the cyclic amine moiety in these formulae introduces a third contiguous chiral center into the molecules. Although the present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates, it is preferred that compounds of the invention exist as single enantiomers at the chiral center introduced by the cyclic moiety. It is especially preferred that the three contiguous chiral centers in the core structure of compounds of Formulae I – III and V-VII exist with the absolute configurations illustrated in the following Figure (ii):



(ii)

Furthermore, the skilled artisan will appreciate that additional chiral centers are created in compounds of Formulae I-IV and VII when variable R^3 differs from variable R^4 or when variable R^5 differs from variable R^6 . The present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates. Compounds of Formulae I-IV and VII where R^4 and R^6 are hydrogen and R^3 and R^5 are other than hydrogen are preferred. It is also preferred that compounds of Formulae I-IV and VII where R^4 and R^6 are hydrogen and R^3 and R^5 are other than hydrogen exist in the following absolute configuration:



The single enantiomers or diastereomers may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single

enantiomers or diastereomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques at any convenient point in the synthesis of compounds of the invention. Single enantiomers and diastereomers of compounds of the invention are a preferred embodiment of the invention.

5 It will be understood by the skilled reader that many or all of the compounds of Formulae I-III and V-VII are capable of forming salts with any of a number of inorganic and organic acids. In all cases, the pharmaceutically acceptable salts of all of the compounds of Formula I, and acid addition salts of the compounds of Formulae II, III, and V-VII are included in the names of them. Methods for preparation of
10 pharmaceutically acceptable salts of compounds of the present invention are well known to the skilled artisan (See: Stahl, P. Heinrich and Wermuth, Camille G., "Handbook of Pharmaceutical Salts: Properties, Selection and Use," VCHA/Wiley-VCH (2002); and Berge, S.M., Bighley, L.D., and Monkhouse, D.C. "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, 66(1), (January 1977)). Preferred salts in all cases are those
15 formed with hydrochloric acid or trifluoroacetic acid.

Although all of the compounds of Formula I are useful inhibitors of BACE, certain classes of compounds are preferred. The following paragraphs describe such preferred classes:

- 20 aa) R^1 is C_1 - C_{10} alkyl optionally substituted with C_1 - C_6 alkoxy, oxo, or up to three times with fluoro;
- ab) R^1 is C_1 - C_6 alkyl optionally substituted with C_1 - C_6 alkoxy;
- ac) R^1 is methyl optionally substituted with methoxy;
- ad) R^1 is methyl;
- ae) R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or
25 furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of
30 halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^7$;
- af) R^1 is benzyl;
- ag) R^2 is benzyl optionally mono- or difluorinated in the phenyl ring;

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- ah) R^2 is benzyl;
- ai) R^2 is 3-fluorobenzyl;
- aj) R^2 is 3,5-difluorobenzyl;
- ak) R^2 is benzyl optionally monosubstituted in the 3-position of the phenyl
5 ring with a substituent selected from the group consisting of halo, C_1 - C_6
alkyl optionally substituted in the alkyl chain up to three times with fluoro,
 C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times
with fluoro, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to
three times with fluoro, and C_3 - C_8 cycloalkoxy; or disubstituted in the
10 phenyl ring with a first substituent selected from the group consisting of
halo and trifluoromethoxy and a second substituent selected from the
group consisting of halo, C_1 - C_6 alkyl optionally substituted in the alkyl
chain up to three times with fluoro, C_1 - C_6 alkoxy optionally substituted in
the alkyl chain up to three times with fluoro, C_1 - C_6 alkylthio optionally
15 substituted in the alkyl chain up to three times with fluoro, and C_3 - C_8
cycloalkoxy;
- al) R^2 is 3-propoxybenzyl;
- am) R^2 is 3-(2-fluoroethoxy)benzyl;
- an) R^2 is 5-fluoro-3-propoxybenzyl;
- ao) R^3 is hydrogen;
- 20 ap) R^3 is methyl or ethyl;
- aq) R^4 is hydrogen;
- ar) R^3 is methyl or ethyl, and R^4 is hydrogen;
- as) R^5 is R^9 or $-(CH_2)_{0-2}-OR^9$;
- 25 at) R^5 is $-(CH_2)_{0-2}-OR^9$;
- au) R^5 is OR^9 ;
- av) R^6 is hydrogen;
- aw) R^5 is OR^9 and R^6 is hydrogen;
- ax) R^9 is C_1 - C_{10} alkyl optionally substituted with 1-6 fluorine atoms or C_1 - C_6
30 alkoxy;
- ay) R^9 is neopentyl;
- az) R^9 is neopentyl substituted with 1-6 fluorine atoms;

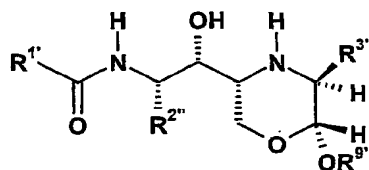
-27-

- ba) R^9 is $-(CH_2)_{0-4}-R^{10}$;
 bb) R^9 is $-CH_2-R^{10}$;
 bc) R^{10} is C_3-C_8 cycloalkyl optionally substituted with up to 4 fluorine atoms;
 bd) R^{10} is cyclohexyl;
 5 be) R^{10} is adamantyl;
 bf) The compound of Formula I is a free base;
 bg) The compound of Formula I is a pharmaceutically acceptable salt;
 bh) The compound of Formula I is the hydrochloride salt.

Preferred embodiments of the invention include all combinations of paragraphs aa)-bh).

- 10 Especially preferred compounds of Formula I are those where R^1 is C_1-C_6 alkyl optionally substituted with C_1-C_6 alkoxy and R^2 is benzyl; 3-fluorobenzyl; 3,5-difluorobenzyl; or benzyl substituted in the 3-position of the phenyl ring with C_1-C_6 alkoxy optionally substituted up to three times with fluoro, C_1-C_6 alkyl optionally substituted up to three times with fluoro, C_1-C_6 alkylthio optionally substituted up to three times with fluoro, or
 15 C_3-C_8 cycloalkoxy and optionally further substituted in the 5-position with fluoro.

A preferred subgenus of compounds of Formula I are compounds of Formula I(a):



I(a)

- 20 where;

$R^{1'}$ is hydrogen; benzyl; or C_1-C_{10} alkyl optionally substituted with C_1-C_6 alkoxy, oxo, or up to six times with fluoro;

- $R^{2''}$ is benzyl optionally monosubstituted in the 3-position of the phenyl ring with a substituent selected from the group consisting of halo, C_1-C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro, C_1-C_6 alkoxy optionally substituted in the
 25 alkyl chain up to three times with fluoro, C_1-C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro, and C_3-C_8 cycloalkoxy; or benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo and trifluoromethoxy and a second substituent selected from the group consisting of halo, C_1-

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C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro, and C₃-C₈ alkoxy;

5 R^{3'} is hydrogen or C₁-C₄ alkyl;

 R^{9'} is C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms; C₁-C₄ alkyl substituted with tetrahydrofuryl, tetrahydropyranyl, or C₃-C₈ cycloalkyl optionally substituted with up to 4 fluoro atoms; or a pharmaceutically acceptable salt thereof. Especially preferred compounds of Formula I(a) are those where R^{1'} is C₁-C₆ alkyl
10 optionally substituted with C₁-C₆ alkoxy; R^{2''} is 3,5-difluorobenzyl or benzyl substituted in the 3-position of the phenyl ring with C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro, or C₃-C₈ cycloalkoxy, and optionally further substituted in the
15 5-position with fluoro; and R^{3'} is methyl or ethyl.

 Another embodiment of the present invention is compounds of Formula I where:

 R¹ is C₁-C₆ alkyl;

 R² is C₁-C₃ alkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, C₁-C₆ alkoxy optionally substituted
20 in the alkyl chain with C₃-C₇ cycloalkyl, and C₁-C₆ alkylthio optionally substituted in the alkyl chain with C₃-C₇ cycloalkyl, or benzyl optionally disubstituted in the phenyl ring with a first substituent independently selected from halo and a second substituent independently selected from halo, C₁-C₆ alkoxy optionally substituted in the alkyl chain with C₃-C₇ cycloalkyl, and C₁-C₆ alkylthio optionally substituted in the alkyl chain with
25 C₃-C₇ cycloalkyl;

 R³ is hydrogen or C₁-C₆ alkyl;

 R⁴ is hydrogen or C₁-C₆ alkyl;

 R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

30 R⁵ is hydrogen, R⁹, or -(CH₂)₀₋₂-OR⁹;

 R⁶ is hydrogen or phenyl;

 G is O or S(O)₀₋₂;

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R⁹ is C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms, C₁-C₁₀ 1, C₂-C₆ alkenyl, or -(CH₂)₀₋₃-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl, tetrahydrofuryl, or phenyl each optionally substituted with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, trifluoromethyl, and trifluoromethoxy, or R¹⁰ is adamantyl;
5 or a pharmaceutically acceptable salt thereof.

Although all of the compounds of Formula II are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:

- 10 bi) R¹ is C₁-C₁₀ alkyl optionally substituted with C₁-C₆ alkoxy, oxo, or up to three times with fluoro;
- bj) R¹ is C₁-C₆ alkyl optionally substituted with C₁-C₆ alkoxy;
- bk) R¹ is methyl optionally substituted with methoxy;
- bl) R¹ is methyl;
- bm) R^{2'} is benzyl optionally mono- or difluorinated in the phenyl ring;
- 15 bn) R^{2'} is benzyl;
- bo) R^{2'} is 3-fluorobenzyl;
- bp) R^{2'} is 3,5-difluorobenzyl;
- bq) R^{2'} is benzyl substituted in the phenyl ring with -OR¹², halo, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro, and C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro, C₃-C₈ cycloalkoxy, and optionally further substituted with fluoro;
- 20 br) R^{2'} is 3-propoxybenzyl;
- bs) R^{2'} is 3-(2-fluoroethoxy)benzyl;
- bt) R^{2'} is 5-fluoro-3-propoxybenzyl;
- bu) R^{2'} is 3-hydroxybenzyl;
- bv) R^{2'} is 5-fluoro-3-hydroxybenzyl;
- bw) R³ is hydrogen;
- 30 bx) R³ is methyl or ethyl;
- by) R⁴ is hydrogen;
- bz) R³ is methyl or ethyl, and R⁴ is hydrogen;

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- ca) R^5 is R^9 or $-(CH_2)_{0-2}-OR^9$;
cb) R^5 is $-(CH_2)_{0-2}-OR^9$;
cc) R^5 is OR^9 ;
cd) R^6 is hydrogen;
5 ce) R^5 is OR^9 and R^6 is hydrogen;
cf) R^9 is C_1-C_{10} alkyl optionally substituted with 1-6 fluorine atoms or C_1-C_6 alkoxy;
cg) R^9 is neopentyl;
ch) R^9 is neopentyl substituted with 1-6 fluorine atoms;
10 ci) R^9 is $-(CH_2)_{0-4}-R^{10}$;
cj) R^9 is $-CH_2-R^{10}$;
ck) R^{10} is cyclohexyl;
cl) R^{10} is adamantyl;;
cm) R^{11} is a carbamate protecting group;
15 cn) R^{11} is tert-butoxycarbonyl;
co) R^{12} is hydrogen;
cp) R^{12} is benzyl.

Preferred compounds of Formula II include all combinations of paragraphs bi) – cp).

Especially preferred compounds of Formula II are those where R^1 is C_1-C_6 alkyl

- 20 optionally substituted with C_1-C_6 alkoxy, $R^{2'}$ is benzyl, 3-fluorobenzyl, 3,5-difluorobenzyl, or benzyl substituted in the 3-position of the phenyl ring with $-OR^{12}$, C_1-C_6 alkoxy optionally substituted up to three times with fluoro, C_1-C_6 alkyl optionally substituted up to three times with fluoro, C_3-C_8 cycloalkoxy, C_1-C_6 alkylthio optionally substituted up to three times with fluoro and optionally further substituted in the 5-
25 position with fluoro, R^3 is hydrogen, methyl, or ethyl, R^4 and R^6 are both hydrogen, and R^5 is OR^9 .

Although all of the compounds of Formula III are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:

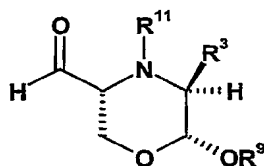
- 30 cq) $R^{2'}$ is benzyl optionally mono- or difluorinated in the phenyl ring;
cr) $R^{2'}$ is benzyl;
cs) $R^{2'}$ is 3-fluorobenzyl;
ct) $R^{2'}$ is 3,5-difluorobenzyl;

- cu) $R^{2'}$ is benzyl substituted in the phenyl ring with $-OR^{12}$, halo, C_1-C_6 alkoxy optionally substituted up to three times with fluoro, C_1-C_6 alkyl optionally substituted up to three times with fluoro, C_1-C_6 alkylthio optionally substituted up to three times with fluoro, or C_3-C_8 cycloalkoxy, and optionally further substituted with fluoro.;
- 5 cv) $R^{2'}$ is 3-propoxybenzyl;
- cw) $R^{2'}$ is 3-(2-fluoroethoxy)benzyl;
- cx) $R^{2'}$ is 5-fluoro-3-propoxybenzyl;
- cy) $R^{2'}$ is 3-hydroxybenzyl;
- 10 cz) $R^{2'}$ is 5-fluoro-3-hydroxybenzyl;
- da) R^3 is hydrogen;
- db) R^3 is methyl or ethyl;
- dc) R^4 is hydrogen;
- dd) R^3 is methyl or ethyl, and R^4 is hydrogen;
- 15 de) R^5 is R^9 or $-(CH_2)_{0-2}-OR^9$;
- df) R^5 is $-(CH_2)_{0-2}-OR^9$;
- dg) R^5 is OR^9 ;
- dh) R^6 is hydrogen;
- di) R^5 is OR^9 and R^6 is hydrogen;
- 20 dj) R^9 is C_1-C_{10} alkyl optionally substituted with 1-6 fluorine atoms;
- dk) R^9 is neopentyl;
- dl) R^9 is neopentyl substituted up to six times with fluoro;
- dm) R^9 is $-CH_2-R^{10}$;
- dn) R^{10} is cyclohexyl;
- 25 do) R^{10} is adamantyl;
- dp) $R^{11'}$ is hydrogen;
- dq) $R^{11'}$ is a carbamate protecting group;
- dr) $R^{11'}$ is tert-butoxycarbonyl;
- ds) R^{12} is hydrogen;
- 30 dt) R^{12} is a silyl group;
- du) R^{12} is tert-butyldimethylsilyl;
- dv) R^{12} is benzyl.

Preferred compounds of Formula III include all combinations of paragraphs cq) – dv). Especially preferred compounds of Formula III are those where $R^{2'}$ is benzyl, 3-fluorobenzyl, 3,5-difluorobenzyl, or benzyl substituted in the 3-position of the phenyl ring with $-OR^{12}$, halo, C_1-C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro, C_1-C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C_1-C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro, or C_3-C_8 cycloalkoxy, and optionally further substituted in the 5-position with fluoro, R^3 is hydrogen, methyl, or ethyl, R^4 and R^6 are both hydrogen, R^5 is OR^9 , and R^{11} and R^{12} are both hydrogen.

- Although all of the compounds of Formula IV are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:
- dw) R^3 is hydrogen;
 - dx) R^3 is methyl or ethyl;
 - dy) R^4 is hydrogen;
 - dz) R^3 is methyl or ethyl, and R^4 is hydrogen;
 - ea) R^5 is $-OR^9$;
 - eb) R^6 is hydrogen;
 - ec) R^9 is C_1-C_{10} alkyl optionally substituted with 1-6 fluorine atoms or C_1-C_6 alkoxy;
 - ed) R^9 is neopentyl optionally substituted up to six times with fluoro;
 - ee) R^9 is $-(CH_2)_{0-4}-R^{10}$;
 - ef) R^9 is $-CH_2-R^{10}$;
 - eg) R^{10} is cyclohexyl;
 - eh) R^{10} is adamantyl;
 - ei) R^{11} is a carbamate protecting group;
 - ej) R^{11} is tert-butoxycarbonyl.

A preferred subgenus of intermediates of Formula IV are compounds of Formula IV(a):



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IV(a)

where R^3 , R^9 , and R^{11} are as previously defined. Preferred compounds of Formula IV(a) are those where R^3 is hydrogen, methyl, or ethyl.

Although all of the compounds of Formula V are useful intermediates for the
5 preparation of BACE inhibitors, certain of the compounds are preferred:

- ek) $R^{2'}$ is benzyl optionally mono- or difluorinated in the phenyl ring;
- el) $R^{2'}$ is benzyl;
- em) $R^{2'}$ is 3-fluorobenzyl;
- en) $R^{2'}$ is 3,5-difluorobenzyl;
- 10 eo) $R^{2'}$ is benzyl substituted in the phenyl ring with $-OR^{12}$, halo, C_1-C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro, C_1-C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C_1-C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro, or C_3-C_8 cycloalkoxy, and optionally further substituted with fluoro;
- 15 ep) $R^{2'}$ is 3-propoxybenzyl;
- eq) $R^{2'}$ is 3-(2-fluoroethoxy)benzyl;
- er) $R^{2'}$ is 5-fluoro-3-propoxybenzyl;
- es) $R^{11'}$ is hydrogen or a carbamate protecting group;
- 20 et) $R^{11'}$ is hydrogen;
- eu) $R^{11'}$ is a carbamate protecting group;
- ev) $R^{11'}$ is tert-butoxycarbonyl;
- ew) R^{11} is benzyl;
- ex) $R^{12'}$ is benzyl;
- 25 ey) R^{11} and $R^{12'}$ are all benzyl;

Although all of the compounds of Formula VI are useful intermediates for the
preparation of BACE inhibitors, certain of the compounds are preferred:

- ez) R^1 is C_1-C_{10} alkyl optionally substituted with C_1-C_6 alkoxy, oxo, or up to three times with fluoro;
- 30 fa) R^1 is C_1-C_6 alkyl optionally substituted with C_1-C_6 alkoxy;
- fb) R^1 is methyl optionally substituted with methoxy;
- fc) R^1 is methyl.

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- fd) R^{2'} is benzyl optionally mono- or difluorinated in the phenyl ring;
fe) R^{2'} is benzyl;
ff) R^{2'} is 3-fluorobenzyl;
fg) R^{2'} is 3,5-difluorobenzyl;
5 fh) R^{2'} is benzyl substituted in the phenyl ring with -OR¹², halo, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro, or C₃-C₈ cycloalkoxy, and optionally further substituted with fluoro;
10 fi) R^{2'} is 3-propoxybenzyl;
fj) R^{2'} is 3-(2-fluoroethoxy)benzyl;
fk) R^{2'} is 5-fluoro-3-propoxybenzyl;
fl) R^{2'} is 3-hydroxybenzyl;
15 fm) R^{2'} is 5-fluoro-3-hydroxybenzyl;
fn) R^{11'} is hydrogen or a carbamate protecting group;
fo) R^{11'} is hydrogen;
fp) R^{11'} is a carbamate protecting group;
fq) R^{11'} is tert-butoxycarbonyl;
20 fr) R^{12'} is benzyl.

Although all of the compounds of Formula VII are useful intermediates for the preparation of BACE inhibitors, certain of the compounds are preferred:

- fs) R^{2'} is benzyl optionally mono- or difluorinated in the phenyl ring;
ft) R^{2'} is benzyl;
25 fu) R^{2'} is 3-fluorobenzyl;
fv) R^{2'} is 3,5-difluorobenzyl;
fw) R^{2'} is benzyl substituted in the phenyl ring with -OR¹², halo, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro, or C₃-C₈ cycloalkoxy, and optionally further substituted with fluoro;
30

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- fx) R^{2'} is 3-propoxybenzyl;
fy) R^{2'} is 3-(2-fluoroethoxy)benzyl;
fz) R^{2'} is 5-fluoro-3-propoxybenzyl;
ga) R^{2'} is 3-hydroxybenzyl;
5 gb) R^{2'} is 5-fluoro-3-hydroxybenzyl;
gc) R³ is hydrogen;
gd) R³ is methyl or ethyl;
ge) R⁴ is hydrogen;
gf) R³ is methyl or ethyl, and R⁴ is hydrogen; where R¹¹, R^{11'}, and R¹² are as
10 previously defined.

The compounds of Formula I are inhibitors of BACE. It is preferred the compound of Formula I selectively inhibits BACE1 relative to BACE2. Thus, the present invention also provides a method of inhibiting BACE in a mammal that comprises administering to a mammal in need of said treatment a BACE-inhibiting amount of a
15 compound of Formula I. It is preferred that the mammal to be treated by the administration of the compounds of Formula I is human.

As inhibitors of BACE, the compounds of the present invention are useful for suppressing the production of A- β peptide, and therefore for the treatment of disorders resulting from excessive A- β peptide levels due to over-production and/or reduced
20 clearance of A- β peptide. The compounds of Formula I are therefore believed to be useful in treating or preventing Alzheimer's disease, mild cognitive impairment, Down's Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias such as: dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia
25 associated with progressive supranuclear palsy, dementia associated cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the present invention may be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to
30 provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

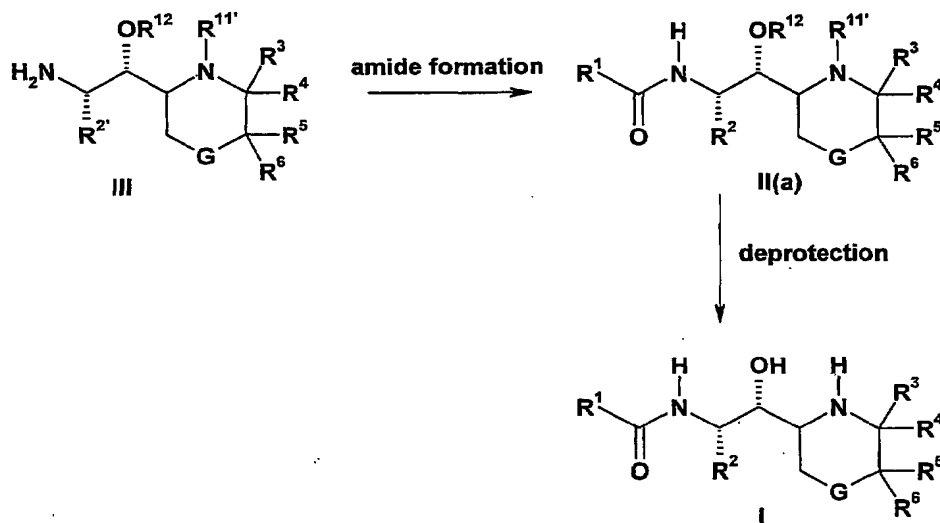
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Some stereochemical centers have been specified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, or diastereomers may be separated at any convenient point in the synthesis of compounds of

5 Formula I.

The compounds of Formula I may be prepared as described in Scheme I where variables G, R¹, R², R^{2'}, R³, R⁴, R⁵, R⁶, R^{11'}, and R¹² are as previously defined:

Scheme I



10 The amine of Formula III is reacted under standard amide forming conditions well known to the skilled artisan to provide compounds of Formula II (for example, see WO 03/040096 and WO 04/024081). An appropriate carboxylic acid of Formula R¹-COOH or an equivalent thereof, such as the sodium or, preferably, potassium carboxylate salt is reacted with a peptide coupling agent such as dicyclohexylcarbodiimide (DCC), 1-(3-

15 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), or *n*-propylphosphonic anhydride, and an appropriate amine such as N-methylmorpholine or triethylamine, in a suitable solvent such as dichloromethane, dimethylformamide (DMF) or tetrahydrofuran (THF) to provide the compound of Formula II. If necessary or desired, an additive such as 4-(dimethylamino)pyridine and/or 1-hydroxybenzotriazole or

20 equivalents thereof may be added to the reaction mixture to facilitate the reaction. Alternatively, other carboxylic acid equivalents, including acylating agents, such as an

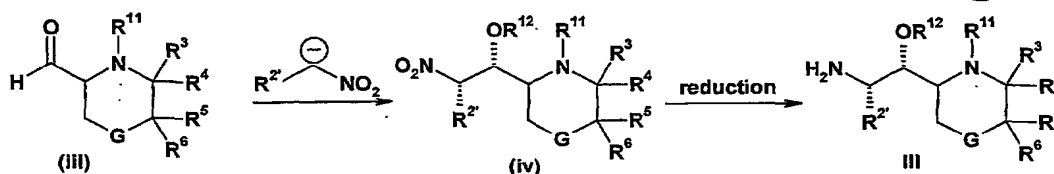
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appropriate acylimidazole, or a mixed anhydride, such as formic acetic anhydride, or an appropriate acid halide may be reacted directly with the amine of Formula III to provide the desired amide of Formula II. The requisite carboxylic acids, carboxylic acid salts, acylating agents, and mixed anhydrides are either commercially available or may be prepared from commercially available materials by methods well known to the skilled artisan. (For example, See: Comprehensive Organic Transformations, Larock, Wiley-VCH Publishers, Inc., New York, (1999); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985)). The skilled artisan will appreciate that any functional group transformations, for example converting an alcohol to an ether, may be performed at any convenient point in the synthesis to provide compounds of Formula I.

The conditions for deprotection of compounds of Formula II to provide compounds of Formula I depend on the nature of variables $R^{11'}$ and R^{12} . The deprotection conditions are those well known to the skilled artisan and are described in the literature. (For example, see: Greene and Wuts, Protective Groups in Organic Synthesis, Third Edition, Chapters 2 and 7, John Wiley and Sons Inc., (1999)). Depending upon the nature of variables R^{11} and R^{12} , they may both be removed in a single reaction, for example by treatment with acid or under hydrogenation conditions, or may be removed sequentially as necessary or desired. Further, if salts of compounds of the invention are desired, an appropriate free base of Formula I is simply reacted with an appropriate pharmaceutically acceptable acid in a suitable solvent under standard conditions to provide a pharmaceutically acceptable salt of a compound of Formula I. The skilled artisan will appreciate that, depending on the nature of variables $R^{11'}$ and R^{12} , the deprotection and salt forming steps may occur simultaneously to provide a pharmaceutically acceptable salt of a compound of Formula I in a single step. The skilled artisan will appreciate that in instances where both $R^{11'}$ and R^{12} are hydrogen, no deprotection step is required to provide compounds of Formula I. The process of Scheme I is a further embodiment of the present invention, and the process where $R^{11'}$ and R^{12} are both hydrogen is a preferred embodiment.

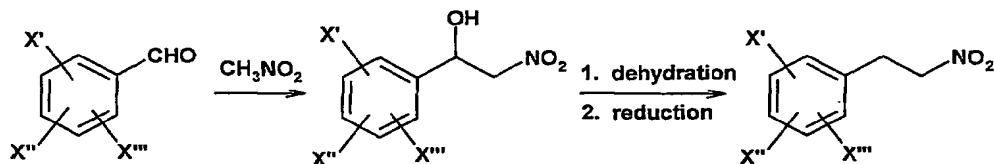
Intermediates of Formula III may be prepared as described in the following scheme where G, R^1 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{11} , and R^{12} are as previously defined.

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Scheme II

Aldehyde (iii) is reacted with the anion of an appropriately substituted nitroalkane to provide the corresponding nitroethane (iv). The nitroethane is reduced under standard chemical or hydrogenation reducing conditions to provide compounds of Formula III. (See: Comprehensive Organic Transformations, Larock, Wiley-VCH Publishers, Inc., New York, (1999); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985)) The skilled artisan will appreciate that the hydroxy moiety generated by the anion addition in the first step of Scheme II may be protected under standard conditions either before or after the reduction step as necessary or desired. (For example, see: Greene and Wuts, Protective Groups in Organic Synthesis, Third Edition, Chapter 2, John Wiley and Sons Inc., (1999)). The requisite anions are prepared by treating the appropriately substituted nitroalkane with a suitable base at low temperature. The requisite appropriately substituted nitroalkanes are either commercially available or may be prepared from commercially available starting materials. (For example, see: Comprehensive Organic Transformations, Larock, Wiley-VCH Publishers, Inc., New York, (1999); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985)) The aldehydes of Formula (iii) represent a further embodiment of the present invention.

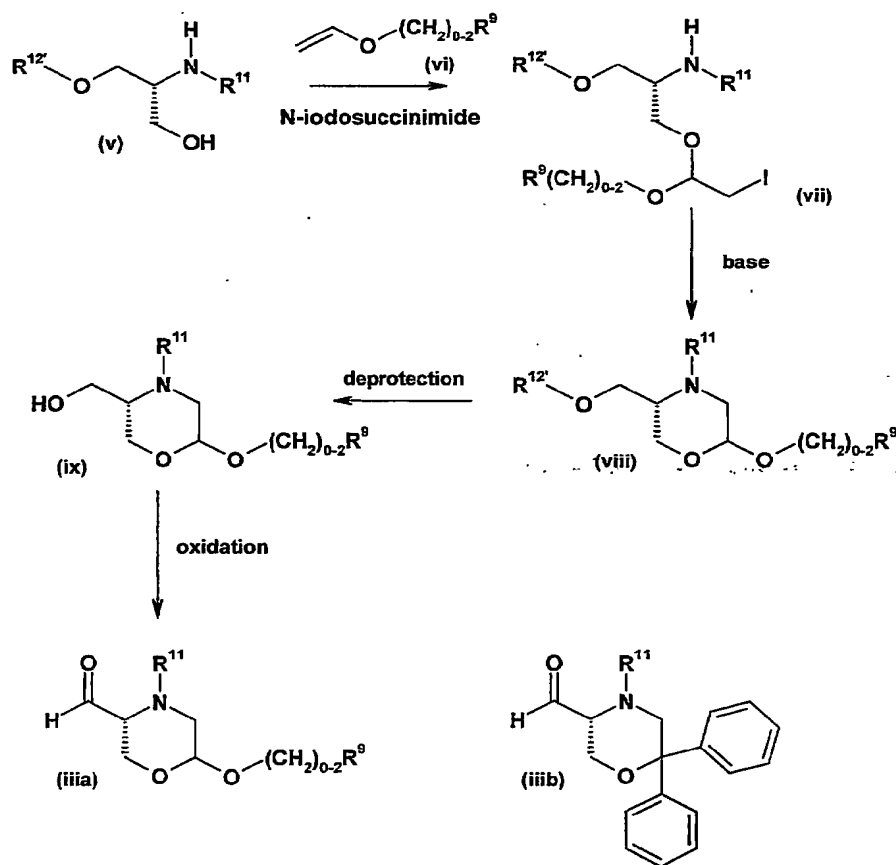
Where R² is an appropriately substituted benzyl group, the requisite nitroalkanes may be prepared essentially as described in the following scheme where X', X'', and X''' are optional substituents for the phenyl group of the benzyl moiety as defined for variables R² and R^{2'}.

Scheme III

An appropriately substituted benzaldehyde is reacted with nitromethane in the presence of a suitable base to provide the corresponding 1-nitro-2-hydroxy-2-phenylethane. The molecule is dehydrated and the corresponding double bond reduced under standard conditions to provide the desired 1-nitro-2-phenylethane. The skilled artisan will appreciate that the nitromethane addition and dehydration may occur spontaneously in a single step depending upon the reaction conditions employed.

The requisite aldehydes (iii) may be prepared by standard synthetic methodology well known to the skilled artisan. (For example, see: Comprehensive Organic Transformations, Larock, Wiley-VCH Publishers, Inc., New York, (1999); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985)) Certain aldehydes may be prepared as described in the following scheme where R^9 and R^{11} are as previously defined and $R^{12'}$ is an oxygen protecting group.

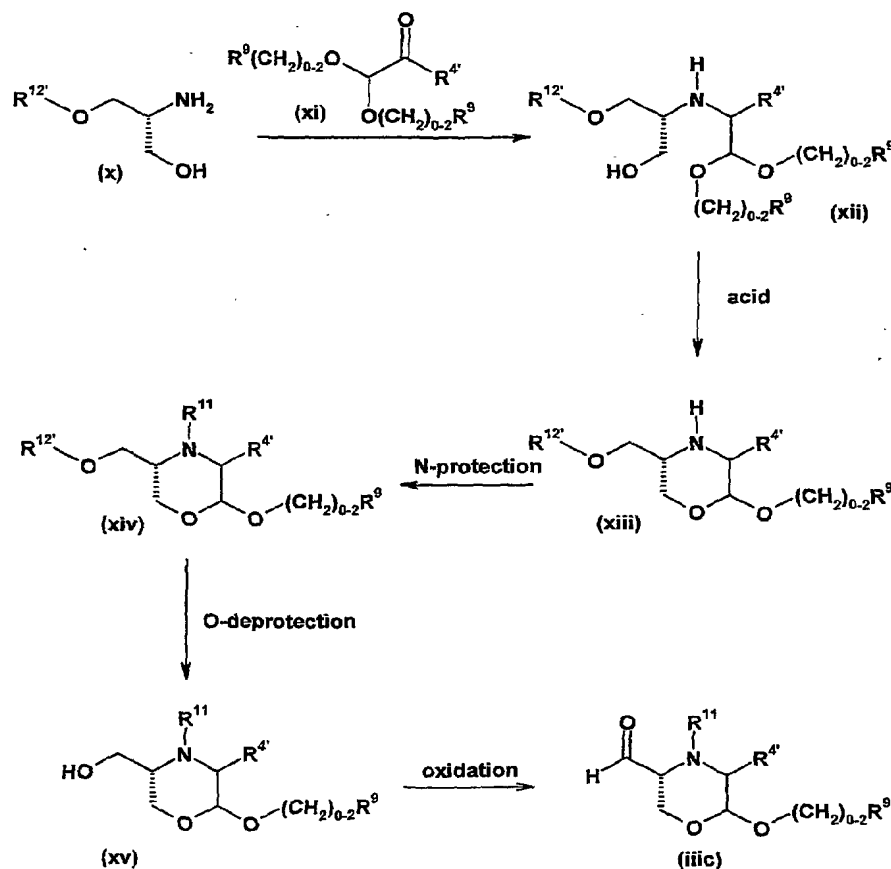
Scheme IV



An appropriately protected serinol (see, e.g., *Chemical Abstracts*, 37, 1743-1746 (1996)) is reacted with a vinyl ether (vi) in the presence of a suitable halogenating agent, such as N-iodosuccinimide, to provide the iodo derivative (vii). This iodo derivative is treated with a suitable base, such as sodium hydride, to provide the cyclic compound (viii). The protected alcohol is deprotected to provide alcohol (ix), which is then oxidized under standard conditions to provide the corresponding aldehyde (iia). Compounds of formula (iib) may be prepared by substituting 1,1-diphenylethylene for the vinyl ether (v).

Additional aldehydes of formula (iii) may be prepared as described in the following scheme where R^9 and R^{11} are as previously defined, $R^{4'}$ is C_1 - C_6 alkyl, and $R^{12'}$ is an oxygen protecting group.

Scheme V

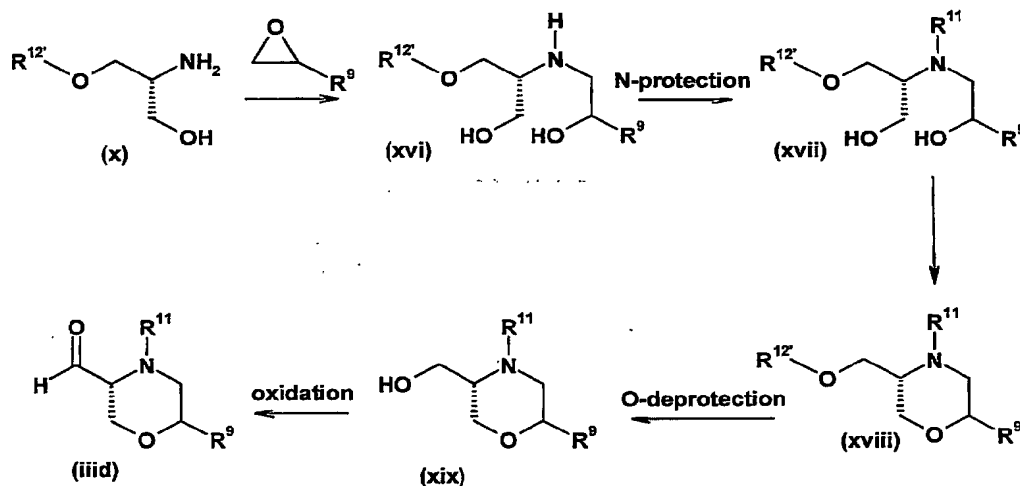


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A protected serinol (x) is condensed with an appropriate α,α -disubstituted ketone (xi) in the presence of acid. The resulting imine or enamine is reduced with an appropriate hydride reducing agent, such as sodium cyanoborohydride, to provide the corresponding amine (xii). This amine is then cyclized in the presence of a suitable acid, such as camphorsulfonic acid, to provide the morpholine (xiii). The morpholine nitrogen is protected under standard conditions to provide intermediate (xiv) which is then O-deprotected to provide alcohol (xv), and then oxidized as described in the previous scheme to provide the desired aldehyde (iiic).

Further aldehydes of formula (iii) may be prepared as described in the following scheme where R^9 and R^{11} are as previously defined and $R^{12'}$ is an oxygen protecting group.

Scheme VI

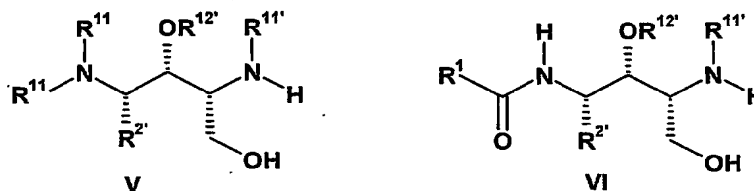


A protected serinol (x) is reacted with an appropriate epoxide or p-toluenesulfonate ester to provide the diol (xvi). The amine moiety is protected under standard conditions and the resulting intermediate (xvii) is reacted with a dehydrating agent, such as 1,1'-azobis(N,N-dimethylformamide) or N,N-tetramethylazodicarboxamide in the presence of tri-n-butylphosphine, to provide the protected morpholine (xviii). This intermediate is then O-deprotected to provide alcohol (xix), which is then oxidized as described in the previous schemes to provide the desired aldehyde (iiid).

Alternatively, the skilled artisan will appreciate that the compounds of Formula I may also be prepared such that the morpholine ring is assembled by applying the

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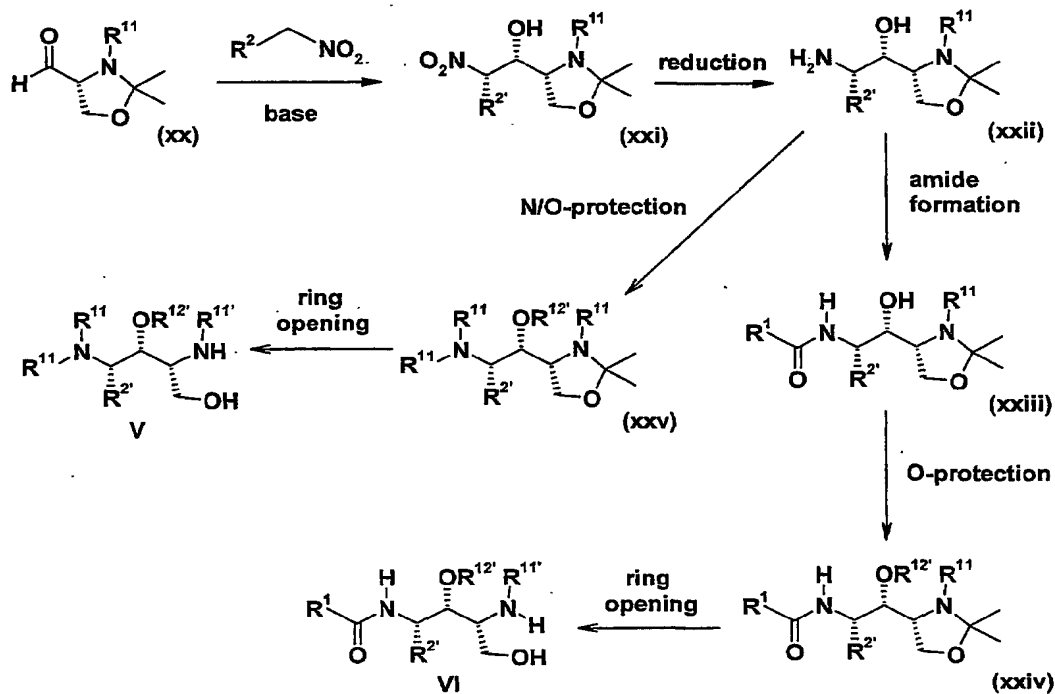
synthetic methodology described in Schemes IV, V, and VI to aminoalcohols of Formula V where R^1 , $R^{2'}$, R^{11} and $R^{12'}$ are as previously defined and R^{11} is independently at each occurrence a nitrogen protecting group, and of Formula VI where R^1 , $R^{2'}$, and $R^{12'}$ are as previously defined and R^{11} is either hydrogen or a nitrogen protecting group:



5

The requisite aminoalcohols V and VI may be prepared as described in the following scheme where variables R^1 , $R^{2'}$, R^{11} , $R^{11'}$, and $R^{12'}$ are as previously defined.

Scheme VII



- 10 An appropriately substituted nitromethane is reacted with an N-protected 4-formyl-2,2-dimethyloxazolidine (xx) in the presence of a suitable base, preferably tetrabutylammonium fluoride, in a suitable solvent, preferably tetrahydrofuran, to provide the nitro derivative (xxi). The amount of base employed is not critical and may be in excess or catalytic amounts depending upon the specific circumstances. Preferably 50 mol % is

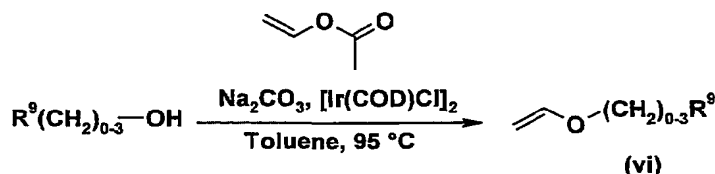
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employed. The nitro group is reduced under standard reducing conditions, such as with sodium borohydride in the presence of nickel(II) chloride, to provide the corresponding amine (xxii). The amine (xxii) is reacted with an appropriate carboxylic acid or carboxylic acid equivalent as previously discussed to provide the desired amide (xxiii).

- 5 The hydroxy group is protected with an oxygen protecting group under standard conditions to provide the protected alcohol (xxiv). The oxazolidine ring is then hydrolyzed under standard conditions to provide the aminoalcohol VI. Alternatively, the amine intermediate (xxii) may be fully protected sequentially, or conveniently the hydroxyl and amino groups may be fully protected with, for example, an appropriate
10 benzyl protecting group to provide intermediate (xxv). The oxazolidine ring is then hydrolyzed as previously described to provide the aminoalcohol V. The skilled artisan will appreciate that the protecting group on the oxazolidine nitrogen may be removed if necessary or desired in the same step as the ring-opening step or in a separate step to provide aminoalcohols of formula V and VI where $R^{11'}$ is hydrogen. The requisite
15 formyloxazolidines (xx) are either commercially available or may be prepared by standard synthetic techniques.

The requisite vinyl ethers (vi) may be prepared from the appropriate alcohols essentially as described by Okimoto, et al., *Journal of the American Chemical Society*, 124, 1590-1591 (2002), as illustrated in the following scheme where R^9 is as previously
20 defined:

Scheme VIII

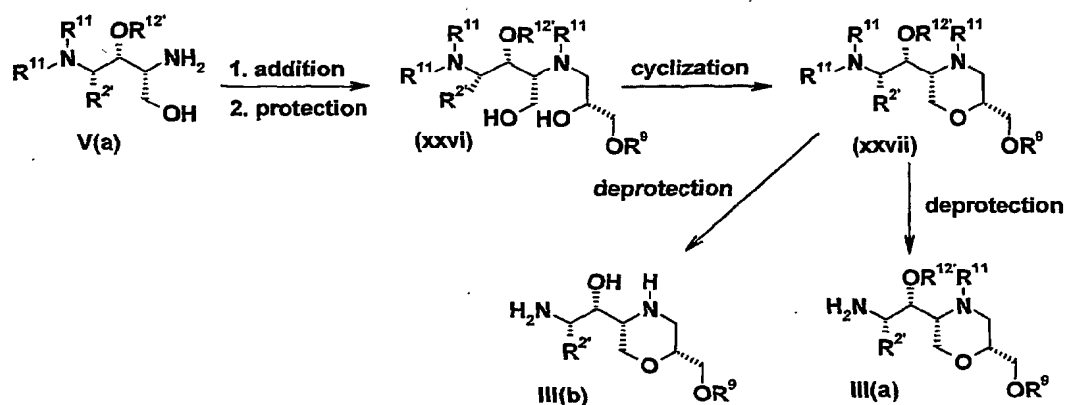


- An appropriate alcohol is reacted with vinyl acetate and sodium carbonate in the presence of chloro(1,5-cyclooctadiene)iridium (I) dimer in a suitable solvent, typically toluene at
25 elevated temperature to provide the vinyl ethers (vi). The requisite alcohols are either commercially available or may be prepared by standard synthetic techniques.

The aminoalcohol intermediate V(a) may be converted into additional intermediates useful for preparing certain compounds of Formula I as illustrated in the following scheme where $R^{2'}$, R^9 , R^{11} , and $R^{12'}$ are as previously defined. Where variable

R^{11} , a nitrogen protecting group, is present in more than one case in a structure in the following scheme, it is understood to be independently selected in each instance.

Scheme IX

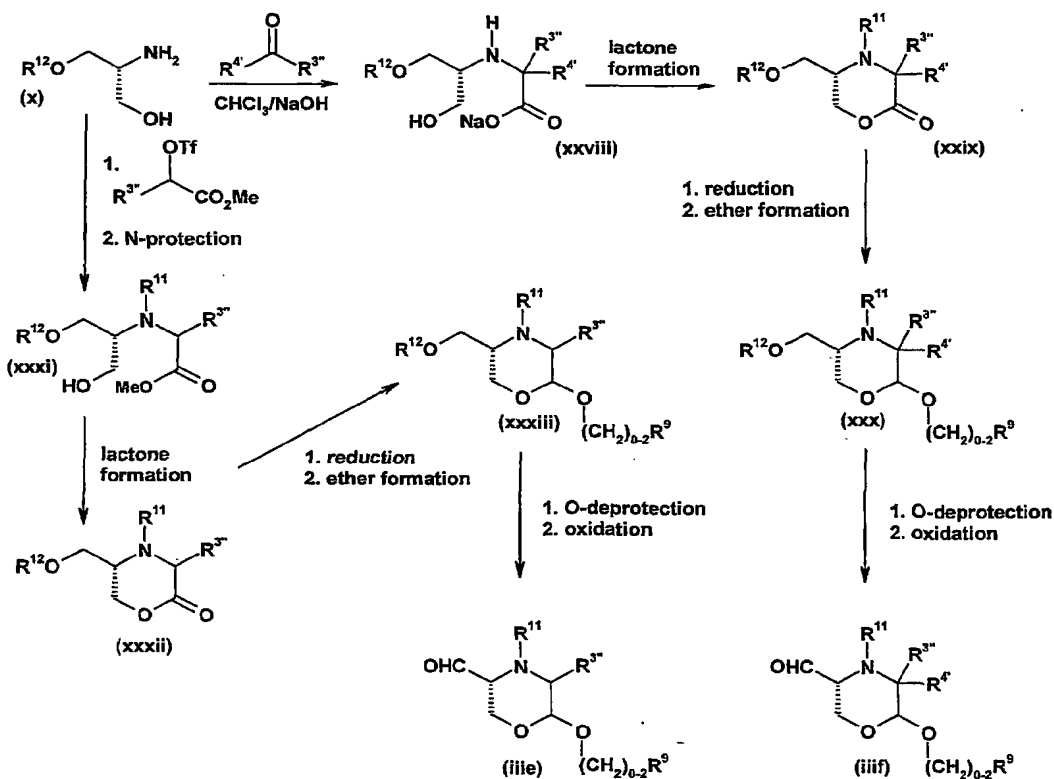


- 5 The aminoalcohol V(a) is reacted with an appropriately substituted epoxide and the addition product is then protected with an appropriate nitrogen protecting group, preferably *tert*-butoxycarbonyl, under standard conditions to provide intermediate (xxvi). This diol intermediate is treated with a dehydrating agent as previously described to provide the protected morpholine (xxvii). This intermediate may be selectively or
- 10 completely deprotected to provide intermediates III(a) or III(b). These intermediates may then be used to prepare additional compounds of Formula I employing deprotection and amide forming synthetic techniques described in the previous schemes. A useful variation of this scheme is to begin with an appropriately substituted epoxide bearing an oxygen protecting group (R^{12}) instead of the moiety (R^9). This protecting group may
- 15 then be removed at any convenient point in the synthesis of compounds of Formula I to provide a hydroxy moiety that may then be substituted under standard conditions to provide additional compounds of Formula I.

Additional aldehydes of formula (iii) useful for the preparation of compounds of the present invention may be prepared as illustrated in the following scheme where R^{11}

20 and R^{12} are as previously defined and $R^{3''}$ and $R^{4'}$ are independently C_1 - C_6 alkyl.

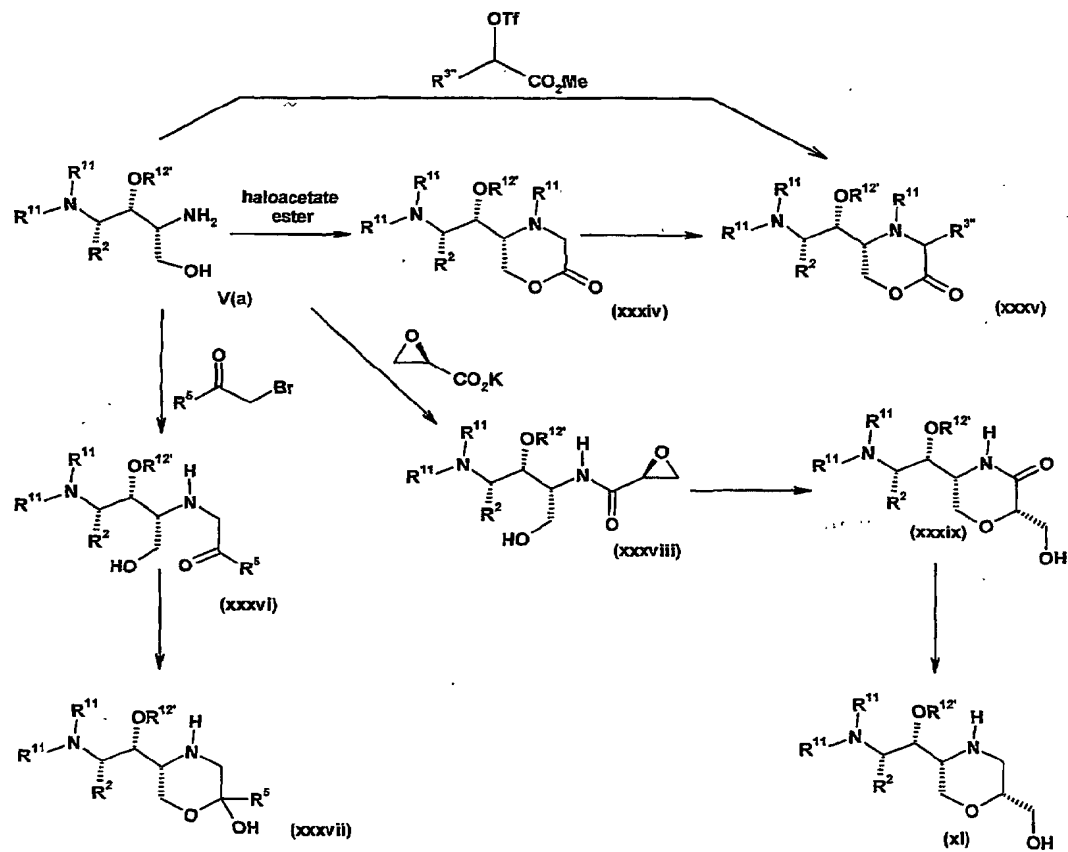
Scheme X



- An appropriately substituted serinol (x) (Novachek, *et al.*, *Tetrahedron Letters*, 37, 1743-1746 (1996)) is reacted with an appropriate ketone and chloroform in the presence of sodium hydroxide essentially as described by Lai (*Synthesis*, 122-123 (1984)) to provide the hydroxycarboxylate (xxviii). The hydroxycarboxylate is then treated under standard ester forming conditions, for example by reaction with dicyclohexylcarbodiimide (DCC), and then the nitrogen protected under standard conditions to prepare lactone (xxix). The carbonyl is reduced by reaction with a hydride reducing agent, such as diisobutylaluminum hydride (DIBALH) and the corresponding alkoxide alkylated with an appropriate reagent to provide ether (xxx). The primary alcohol is then deprotected, if necessary, and oxidized as previously described to provide aldehyde (iiif). In an analogous manner, the appropriately protected serinol (x) is reacted with an appropriate triflate followed by amine protection to provide the hydroxyester (xxxi). The hydroxy group is deprotonated by reaction with a suitable base, for example sodium hydride, to form the lactone (xxxii).

The carbonyl is reduced and alkylated to provide ether (xxxiii) as previously described, and then the protected alcohol is deprotected, if necessary, and oxidized to provide aldehyde (iiie). The skilled artisan will appreciate that the order of these steps may be varied as necessary or desired. The skilled artisan will also appreciate that the synthetic methodology described in the previous scheme may be applied to intermediates V or VI to provide compounds of Formula I.

Additional intermediates useful for the preparation of compounds of Formula I may be prepared as illustrated in the following scheme where R^2 , R^5 , $R^{3''}$, R^{11} and R^{12} are as previously defined. Where variable R^{11} , a nitrogen protecting group, is present more than once in a structure in the following scheme, it is understood to be independently selected in each instance.

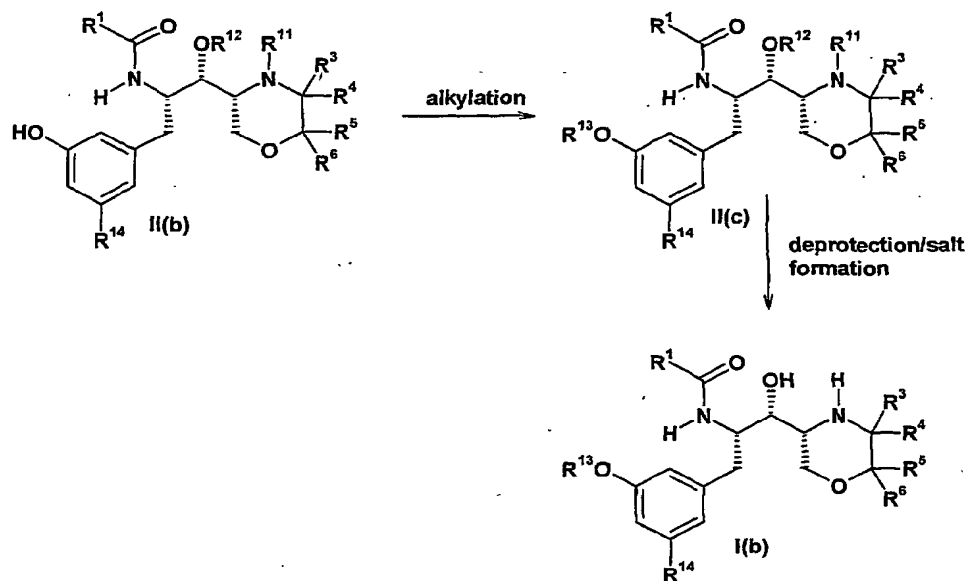


The intermediate aminoalcohol V(a) may be reacted in a number of synthetic pathways to provide more advanced intermediates useful for the preparation of compounds of Formula I. For example, the aminoalcohol V(a) may be treated with an appropriately substituted haloacetate ester, for example methyl or ethyl bromoacetate, to provide the substituted morpholinone (xxxiv). This intermediate may be alkylated under standard conditions to provide the corresponding α -substituted intermediate (xxxv). Alternatively, V(a) may be reacted with an appropriately substituted triflate to provide intermediates of formula (xxxv) directly. Aminoalcohol V(a) may also be treated with an appropriately substituted acetyl compound to provide ketoalcohol (xxxvi). Treatment of this ketoalcohol under standard conditions provides the hemiketal (xxxvii). The aminoalcohol V(a) may also be coupled with oxirane-2-carboxylic acid potassium salt (Organic Synthesis, 75, 37-43) to provide the corresponding amidoalcohol (xxxviii). Treatment of this intermediate with an appropriate base, for example, potassium hexamethyldisilazane or potassium hydride, provides the substituted morpholine (xxxix), which may be subsequently functionalized under standard conditions or the amide carbonyl reduced under standard conditions to provide intermediate (xl). Intermediates (xxxiv), (xxxv), (xxxvii) and (xl), which are further embodiments of the present invention, may be subjected to standard functional group transformation conditions well known to one of ordinary skill in the art, followed by deprotection and coupling reactions described above to provide additional compounds of Formula I. (For example, see: Comprehensive Organic Transformations, Larock, Wiley-VCH Publishers, Inc., New York, (1999); Advanced Organic Chemistry, March, Wiley Interscience, New York, Third Edition, (1985)).

Compounds of Formula I where R^2 is benzyl substituted with a C_1 - C_6 alkoxy moiety optionally further substituted in the alkyl chain with C_3 - C_8 cycloalkyl or up to three times with fluoro may be prepared as described in the following scheme where G, R^1 , R^3 , R^4 , R^5 , R^6 , R^{11} , and R^{12} are as previously defined, R^{13} is C_1 - C_6 alkyl optionally substituted with C_3 - C_8 cycloalkyl or up to three times with fluoro, and R^{14} is hydrogen or fluoro.

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Scheme XII



The phenol II(b) is reacted with a suitable alkylating reagent, such as an alkyl halide, in the presence of a suitable base, such as cesium carbonate, to provide intermediate II(c). This intermediate is then deprotected under standard conditions as previously described to provide a compound of Formula I(b). If necessary or desired, the deprotected compound may be converted to a pharmaceutically acceptable salt under standard conditions. Compounds of Formula II(b), II(c), and I(b) represent preferred embodiments of the present invention.

Preparation 1

3,5-Difluorophenyl nitroethane

1-(3,5-Difluorophenyl)-2-nitroethanol

Add nitromethane (200 mL) to a suspension of potassium carbonate (30 g) and 3,5-difluorobenzaldehyde (200 g) in tetrahydrofuran (600 mL) at room temperature. Stir at room temperature overnight, filter, wash with ethyl acetate and concentrate to give the desired compound as a crude oil (330 g) which is used in the next step without further purification.

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1,3-Difluoro-5-(2-nitrovinyl)-benzene

Add acetic anhydride (160 mL) to a solution of 1-(3,5-difluorophenyl)-2-nitroethanol (330 g) and 4-dimethylaminopyridine (18 g) in dichloromethane (1000 mL), over 30 minutes and stir the reaction mixture overnight. Dilute with dichloromethane (600 mL) and wash with 2% aqueous hydrochloric acid, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, dry (magnesium sulfate) and concentrate. Wash the crude with hexanes to give the desired compound (220 g).

3,5-Difluorophenyl nitroethane

Add portionwise sodium borohydride (12 g) over 1.5 hours to a solution of 1,3-difluoro-5-(2-nitrovinyl)-benzene (100 g) in a mixture of dimethylsulfoxide (400 mL) and acetic acid (80 mL) at room temperature using a water bath to keep the temperature below 30 °C. Dilute with ethyl acetate (1000 mL) and wash with water (600 mL), saturated aqueous sodium bicarbonate (2 x 600 mL), saturated aqueous sodium chloride (600 mL), dry (magnesium sulfate) concentrate and purify (silica gel chromatography, eluting with 3:97 ethyl acetate:hexanes) to give the title compound as a pale yellow liquid (63 g, 62%).

Preparation 2

1-Fluoro-2-(2-vinyloxyethyl)-benzene

Combine 2-(2-fluorophenyl)-ethanol (3.08 g, 22.0 mmol), vinyl acetate (4 mL, 43.3 mmol), anhydrous toluene (22 mL), chloro(1,5-cyclooctadiene)iridium(I) dimer (155 mg, 0.231 mmol), and anhydrous sodium carbonate (1.5 g, 14.2 mmol) in a dry round-bottom flask fitted with a reflux condensor under a nitrogen atmosphere. Heat the resulting mixture to 95 °C for 5 hours. Cool the reaction mixture to room temperature. Vacuum filter the resultant slurry to remove inorganic precipitates, washing the collected solid with hexanes. Concentrate and purify (silica gel chromatography, eluting with hexanes) to give the title compound as a yellow oil (2.64 g, 72%).

¹H-NMR(400 MHz, CDCl₃) δ 7.27-7.18 (m, 2H), 7.10-7.00 (m, 2H), 6.46 (dd, J = 6.8, 14.0 Hz, 1H), 4.20 (dd, J = 1.6, 14.0 Hz, 1H), 4.01 (dd, J = 1.6, 6.4 Hz, 1H), 3.91 (at, J = 7.2 Hz, 2H), 3.02 (at, J = 7.2 Hz, 2H).

The vinyl ethers of Preparations 3-20 may be prepared essentially as described in Preparation 2.

| Prep | Name |
|------|--|
| 3 | (3-Vinyloxypropyl)cyclopentane |
| 4 | Vinyloxymethylcycloheptane |
| 5 | 1-Vinyloxymethyladamantane |
| 6 | Vinyloxymethylcyclohexane |
| 7 | 1-Trifluoromethyl-2-(2-vinyloxyethyl)-benzene |
| 8 | 1-Methyl-3-(2-vinyloxyethyl)-benzene |
| 9 | Vinyloxyethylcyclohexane |
| 10 | Vinyloxymethylcyclopentane |
| 11 | Vinyloxymethylcyclooctane |
| 12 | 4-Vinyloxymethyltetrahydropyran |
| 13 | Trans-1-Methyl-4-vinyloxymethylcyclohexane |
| 14 | 1-Methylvinyloxymethylcyclohexane |
| 15 | 1-Fluorovinyloxymethylcyclohexane |
| 16 | 4-Fluoro-4-vinyloxymethyltetrahydropyran |
| 17 | Cis-1- <u>tert</u> -butyl-3-vinyloxy-cyclobutane |
| 18 | (1R,2S,4S)-1-Isopropyl-4-methyl-2-vinyloxy-cyclohexane |
| 19 | (1S,2R,4R)-1-Isopropyl-4-methyl-2-vinyloxy-cyclohexane |
| 20 | (1S,2R,5S)-6,6-Dimethyl-2-vinyloxymethylbicyclo[3.1.1]-heptane |

Preparation 21

5 3,3-Dimethyl-1-vinyloxybutane

Add chloro(1,5-cyclooctadiene)iridium(I) dimer (0.39 g, 0.59 mmol) to 3,3-dimethylbutan-1-ol (3.00 g, 29.35 mmol), vinyl acetate (10.11 g, 117.42 mmol) and sodium carbonate (1.87 g, 17.61 mmol) in benzene (10 mL) at room temperature. Boil under nitrogen 12 hours. Cool to room temperature and filter. Distill the filtrate and
 10 collect fraction boiling ~125 °C-130 °C. Flush through a silica gel pad with hexanes and concentrate to provide the title compound.

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Preparation 22

3-Methyl-1-vinyloxybutane

The title compound may be prepared essentially as described in Preparation 21 and isolated by fractional distillation (collecting the fraction boiling from ~110 °C to 115 °C) followed by flushing through a silica gel pad with hexanes.

Preparation 23

2,2-Dimethyl-1-vinyloxypropane

Boil 2,2-dimethylpropan-1-ol (2.41 g, 27.34 mmol) and mercury (II) trifluoroacetate (1.17 g, 2.73 mmol) in ethyl vinyl ether (19.71 g, 273.40 mmol) under nitrogen for 2 hours. Concentrate to ~10 mL. Dilute with pentane. Wash with 10% aqueous potassium carbonate and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with pentane) to give the title compound.

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The vinyl ethers of Preparations 24-44 may be prepared essentially as described in Preparation 23 starting with the appropriate alcohols.

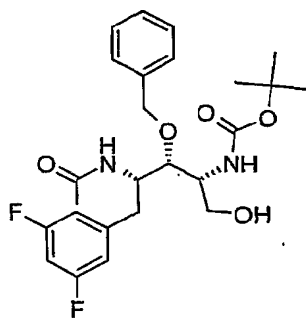
| Prep | Name |
|------|---|
| 24 | Cis-1-Methoxy-4-vinyloxymethylcyclohexane |
| 25 | Trans-1-Methoxy-4-vinyloxymethylcyclohexane |
| 26 | 1,1-Difluoro-4-vinyloxymethylcyclohexane |
| 27 | 4-Methyl-4-vinyloxymethyltetrahydropyran |
| 28 | 2,2-Dimethyl-1-vinyloxypropane |
| 29 | (R)-2-Vinyloxymethyltetrahydrofuran |
| 30 | 1-Vinyloxy-methylbicyclo[2.2.1]heptane |
| 31 | 1-(1-Cyclohexylcyclopropoxy)-ethanol |
| 32 | (1-Vinyloxymethylcyclohexylmethyl)-benzene |
| 33 | 1-Methyl-1-vinyloxymethylcyclopentane |
| 34 | ((R)-1-Vinyloxyethyl)-cyclohexane |
| 35 | (1-Vinyloxymethylcyclopentylmethyl)-benzene |
| 36 | 4-Vinyloxymethylcyclohexanone |

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| | |
|----|---|
| 37 | ((1R,2S)-2-Vinyloxycyclohexyl)-benzene |
| 38 | 2,2-Dimethyl-1-vinyloxypentane |
| 39 | 1,1,1,3,3,3-Hexafluoro-2-methyl-2-vinyloxymethylpropane |
| 40 | 2,2-Dimethyl-1-vinyloxybutane |
| 41 | 2,2-Dimethyl-1-vinyloxypentane |
| 42 | (1-Vinyloxymethylcyclopentyl)-benzene |
| 43 | ((S)-1-Vinyloxyethyl)-cyclohexane |
| 44 | 2,2,4-Trimethyl-1-vinyloxypentane |

Preparation 45

[(1R,2S,3S)-3-Acetylamino-2-benzyloxy-4-(3,5-difluorophenyl)-1-hydroxymethylbutyl]-
carbamic acid tert-butyl ester



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4-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-dimethyloxazolidine-3-
carboxylic acid tert-butyl ester

Dissolve (R)-tert-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (1.60 g, 6.98 mmol) and 1,3-difluoro-5-(2-nitroethyl)-benzene (1.40 g, 7.48 mmol) in dry tetrahydrofuran (14 mL) and add 1 M tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (7.0 mL, 7.0 mmol) in one portion. Stir the resulting mixture for 30 minutes and then dilute with ethyl acetate. Quickly shake the mixture with water and then add a small amount of saturated aqueous sodium chloride. Discard the aqueous phase and wash the organic phase again with water (twice) followed by saturated aqueous sodium chloride. Dry the organic solution over magnesium sulfate (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the coupling product as an approximately ~80:20 mixture of

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diastereomers (2.45 g, 84%). Isolate the major isomer by recrystallization of the diastereomeric mixture from dichloromethane (dichloromethane)/hexanes or diethyl ether/hexanes) to give 1.26 g of the desired compound as a white crystalline solid. MS (ES): 439.3 m/z = [M+Na]

5

(R)-4-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Combine (R)-4-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (1.13 g, 2.71 mmol) and nickel (II) chloride (0.58 g, 4.485 mmol) in dry methanol (30 ml) and add sodium borohydride (0.454 g, 12 mmol) over 1 minute. Stir the resulting mixture for 20 minutes and then add water (3 mL). Concentrate and dissolve the residue in ethyl acetate. Filter the black solution through a pad of Celite® and wash the filter cake with ethyl acetate. Wash the filtrate with water (twice), saturated aqueous sodium chloride, dry (magnesium sulfate), filter, and concentrate to give the desired compound as a white solid (920 mg, 95%).

15

(R)-4-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Dissolve (R)-4-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (920 mg, 2.38 mmol) in dry tetrahydrofuran (20 ml) under an atmosphere of nitrogen. Add to the resulting solution triethylamine (400 μ l, 2.87 mmol) and acetic anhydride (235 μ L, 2.49 mmol). After 1 hour, dilute with ethyl acetate and wash with water (twice), 0.1 N hydrochloric acid, and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography 0:100 to 70:30 ethyl acetate:hexanes) to give the desired compound as a white solid (738 mg, 72% yield).

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MS (ES): 451.2 m/z = [M+Na]

(R)-4-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

30

Suspend (R)-4-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (4.78 g, 11.2 mmol) in dry

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5 tetrahydrofuran (115 ml) under a nitrogen atmosphere and add sodium hydride NaH (60 % weight dispersion in mineral oil, 1.17 g, 29.3 mmol). Stir the resulting mixture for 30 minutes and then add sequentially sodium iodide (600 mg, 4.0 mmol) and benzyl bromide (2.7 mL, 22.7 mmol). Stir the resulting mixture for 2.5 hours and then quench by the addition of a 1:1 mixture of saturated aqueous ammonium chloride and saturated aqueous sodium chloride. Dilute the resulting mixture with ethyl acetate and discard the aqueous phase. Wash the organic phase with saturated aqueous sodium chloride, dry over magnesium sulfate, filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 40:60 ethyl acetate:hexanes) to give the desired compound as a white foam (4.96 g, 85%).

10 MS (ES): 519.2 m/z = [M+H]

Hydrolysis

15 Dissolve (R)-4-[(1S,2S)-2-acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (4.96 g, 9.56 mmol) in methanol (100 mL). To this solution add *p*-toluenesulphonic acid monohydrate (200 mg, 1.05 mmol) and water (150 μ L, 8.33 mmol). Heat the resulting mixture to reflux for 5.5 hours and then dilute the reaction mixture with ethyl acetate. Wash the resulting solution with saturated aqueous sodium bicarbonate followed by saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 90:10 ethyl acetate:hexanes) to give the title compound as a white foam (3.48 g, 76%).

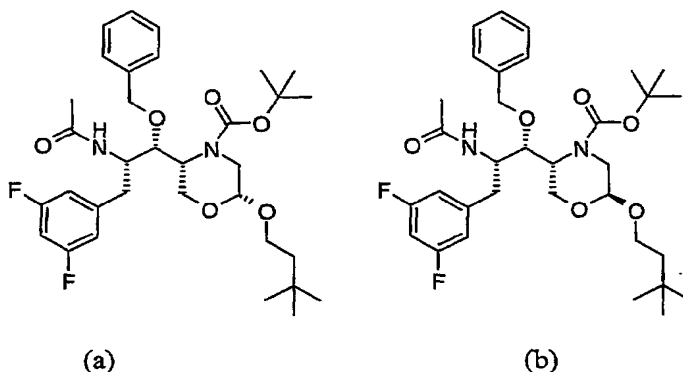
20 MS (ES): 479.4 m/z = [M+H]

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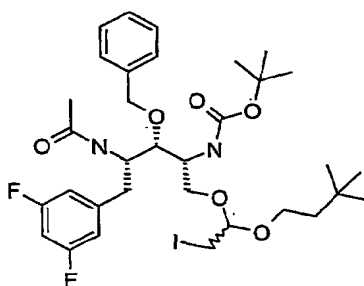
Preparation 46

- (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid tert-butyl ester
- (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid tert-butyl ester

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{(1R,2S,3S)-3-Acetylamino-2-benzyloxy-4-(3,5-difluorophenyl)-1-[1-(3,3-dimethylbutoxy)-2-iodo-ethoxymethyl]-butyl}-carbamic acid tert-butyl ester



5

Dissolve [(1R,2S,3S)-3-acetylamino-2-benzyloxy-4-(3,5-difluorophenyl)-1-hydroxymethyl-butyl]-carbamic acid tert-butyl ester (0.52 g, 1.09 mmol) and 3,3-dimethyl-1-vinyloxybutane (0.15 g, 1.20 mmol) in acetonitrile (6 mL) and add N-iodosuccinimide (0.27 g, 1.20 mmol) at room temperature. Heat in oil bath at 80°C for 2 hours 45 minutes. Cool to room temperature, dilute with ethyl acetate, wash with water or 10% aqueous sodium thiosulfate, saturated aqueous sodium chloride, concentrate and purify (silica gel chromatography, eluting with 10:90 to 30:70 ethyl acetate:hexanes) to give the title compound (0.557 g, 70% yield).

MS (ES): 733.4 m/z = [M+H]

15

Cyclization

Dissolve {(1R,2S,3S)-3-Acetylamino-2-benzyloxy-4-(3,5-difluorophenyl)-1-[1-(3,3-dimethylbutoxy)-2-iodo-ethoxymethyl]-butyl}-carbamic acid tert-butyl ester (0.53 g, 0.72 mmol) in N,N-dimethylformamide (6.5 mL) and add sodium hydride (0.06 g, 1.58 mmol) at room temperature. Heat in an oil bath at 55 °C for 80 minutes. Cool to room

20

temperature and pour into saturated aqueous ammonium chloride. Extract with ethyl acetate, wash with either 1 N lithium chloride or water and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 15:85 to 30:70 ethyl acetate:hexanes) to give:

- 5 (a) less polar diastereomer, 0.186 g, 43% yield. MS (ES): $m/z = 605.5$ [M+H];
and
(b) more polar diastereomer, 0.182 g, 42% yield. MS (ES): $m/z = 605.5$ [M+H]

The compounds of Preparations 47- 107 may be prepared essentially as described
10 in Preparation 46.

| Prep | Compound | MS (ES) [M+H] |
|------|---|------------------------|
| 47 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 577.4 (b) 577.4 |
| 48 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 591.4 (b) 591.4 |
| 49 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-[2-(2-fluorophenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester. (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-[2-(2-fluorophenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 643.4 (b) 643.4 |
| 50 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-cyclopentylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-cyclopentylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester. | (a) 631.5 (b) 631.4 |
| 51 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cycloheptylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cycloheptylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 631.4 (b) 631.5 |

| | | |
|----|--|--|
| 52 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(adamantan-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(adamantan-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 667.2 [M-H] (b) 667.2 [M-H] |
| 53 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-[2-(2-trifluoromethylphenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-[2-(2-trifluoromethylphenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 691.2 [M-H] (b) 691.2 [M-H] |
| 54 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2-m-tolyloethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2-m-tolyloethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 637.3 [M-H] (b) 639.4 [M+H] |
| 55 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 629.2 [M-H] (b) 629.5 [M-H] |
| 56 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclopentylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclopentylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 601.3 [M-H] (b) 601.3 [M-H] |
| 57 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclooctylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclooctylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 643.2 [M-H] (b) 643.2 [M-H] |
| 58 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(tetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(tetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 619.2 [M+H] (b) 617.3 [M-H] |
| 59 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methylcyclohexylmethoxy)- | (a) 631.2 [M+H] (b) 629.2 [M-H] |

| | | |
|----|--|--|
| | morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 60 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-methylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-methylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 631.2 [M+H] (b) 629.2 [M-H] |
| 61 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-fluorocyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-fluoro-cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 633.3 [M-H] (b) 633.3 [M-H] |
| 62 | (a) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-fluorotetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-fluorotetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 635.2 [M-H] (b) 635.2 [M-H] |
| 63 | (a) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3- <u>tert</u> -butylcyclobutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3- <u>tert</u> -butyl-cyclobutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 629.2 [M-H] (b) 629.2 [M-H] |
| 64 | (a) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 657.3 [M-H] (b) 657.3 [M-H] |
| 65 | (a) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | (a) 657.3 [M-H] (b) 657.3 [M-H] |
| 66 | (a) (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester (b) (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1S,2R,5S)-6,6- | (a) 655.2 [M-H] (b) 655.2 [M-H] |

| | | |
|----|---|------------------------------|
| | dimethylbicyclo[3.1.1]hept-2-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 67 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester -Isomer 1 | 547.6 [M-BOC+H] (APCI) |
| 68 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 2 | 547.6 [M-BOC+H] (APCI) |
| 69 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 1 | 647.9 (APCI) |
| 70 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 2 | 647.9 (APCI) |
| 71 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4,4-difluorocyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 653.34 |
| 72 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methyltetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 633.56 |
| 73 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 591.44 |
| 74 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-[(R)-1-(tetrahydrofuran-2-yl)methoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.39 |
| 75 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(bicyclo[2.2.1]hept-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 629.47 |
| 76 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-cyclohexylcyclopropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 643.34 |
| 77 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-benzylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 707.47 |
| 78 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 617.46 |
| 79 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((R)-1-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 631.49 |
| 80 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-benzylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 693.45 |
| 81 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-oxocyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 631.5 |

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| 82 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((1S,2R)-2-phenylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 679.5 |
| 83 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 620.41 |
| 84 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 699.46 |
| 85 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.39 |
| 86 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 620.41 |
| 87 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-phenylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 679.48 |
| 88 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-((S)-1-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 631.53 |
| 89 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2,4-trimethylpentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 633.52 |
| 90 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 591.4 |
| 91 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclohexyloxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 603.4 |
| 92 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-cyclohexyloxy-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 603.4 |
| 93 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 591.4 |
| 94 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.5 |
| 95 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluoro-phenyl)-propyl]-2-(3,3-dimethyl-butoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.5 |
| 96 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 591.4 |

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| 97 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 591.4 |
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Preparation 98

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid tert-butyl ester

- 5 Stir (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.18 g, 0.29 mmol) and 10 % palladium on carbon (0.18 g) in ethanol (5 mL) under hydrogen at room temperature for 14 hours. Filter through Celite® and concentrate to give the title compound (0.148 g, 99.4% yield).
- 10 MS (ES): m/z = 515.4 [M+H]

The compounds of Preparations 99-164 may be prepared essentially as described in Preparation 98.

| Prep | Compound | MS (ES) [M+H] |
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| 99 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 515.4 |
| 100 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 487.4 |
| 101 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 487.4 |
| 102 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 103 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 104 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-[2-(2-fluorophenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 575.2 [M+Na+] |
| 105 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-[2-(2-fluorophenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 575.2 [M+Na+] |
| 106 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-cyclopentylpropoxy)-morpholine-4- | 563.3 [M+Na+] |

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| | carboxylic acid <u>tert</u> -butyl ester | |
| 107 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cycloheptylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 563.3 [M+Na ⁺] |
| 108 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cycloheptylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 599.2 [M+CH ₃ CO ₂ ⁻] |
| 109 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(adamantan-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 601.3 [M+Na ⁺] |
| 110 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(adamantan-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 601.3 [M+Na ⁺] |
| 111 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 549.3 [M+Na ⁺] |
| 112 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 549.3 [M+Na ⁺] |
| 113 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-[2-(2-trifluoromethylphenyl)-ethoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 625.3 [M+Na ⁺] |
| 114 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2- <u>m</u> -tolylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 571.3 [M+Na ⁺] |
| 115 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2- <u>m</u> -tolylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 571.3 [M+Na ⁺] |
| 116 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.2 [M-H] |
| 117 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclopentylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 511.2 [M-H] |
| 118 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclooctylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553.3 [M-H] |
| 119 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(tetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 527.2 [M-H] |
| 120 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-methylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.2 [M-H] |
| 121 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-methylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.2 [M-H] |

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| 122 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-fluorocyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 543.2 [M-H] |
| 123 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-fluorotetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 543.2 [M-H] |
| 124 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3- <u>tert</u> -butylcyclobutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.2 [M-H] |
| 125 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.3 [M-H] |
| 126 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.3 [M-H] |
| 127 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.3 [M-H] |
| 128 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1S,2R,5S)-2-isopropyl-5-methylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.3 [M-H] |
| 129 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]-hept-2-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 565.3 [M-H] |
| 130 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-methoxycyclohexyl-methoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 1 | 557.42 |
| 131 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-methoxycyclohexyl-methoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 2 | 557.43 |
| 132 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 1 | 557.4 (APCI) |
| 133 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(4-methoxycyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomer 2 | 557.44 |
| 134 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4,4-difluorocyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 563.29 |
| 135 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-methyltetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 543.7 (APCI) |
| 136 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.37 |

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| 137 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-[(R)-1-(tetrahydrofuran-2-yl)-methoxy]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 515.29 |
| 138 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(bicyclo[2.2.1]hept-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.4 |
| 139 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-cyclohexylcyclopropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553.32 |
| 140 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-benzylcyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 617.35 |
| 141 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 527.37 |
| 142 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((R)-1-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 541.38 |
| 143 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-benzylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 603.34 |
| 144 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-oxo-cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 541.37 |
| 145 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((1S,2R)-2-phenylcyclohexyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 589.44 |
| 146 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 429.4 [M-BOC+H] (APCI) |
| 147 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 609.41 |
| 148 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 515.3 |
| 149 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 429.4 [M-BOC+H] (APCI) |
| 150 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-phenylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 489.7 [M-BOC+H] (APCI) |
| 151 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-((S)-1-cyclohexylethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 541.39 |
| 152 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2,4-trimethylpentyloxy)-morpholine-4- | 543.42 |

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| | carboxylic acid <u>tert</u> -butyl ester | |
| 153 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 154 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 513.4 |
| 155 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 513.3 |
| 156 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 157 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 515.4 |
| 158 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 515.4 |
| 159 | (2SR,5R)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 160 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-methylbutoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 501.4 |
| 161 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 527.5 |
| 162 | (2SR,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 487.4 |
| 163 | (2RS,5RS)-5-[(1SR,2SR)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-isobutoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 487.4 |
| 164 | (R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 457.2 [M-H] |

Preparation 165

5 N-[(1S,2S)-2-Benzoyloxy-2-[(3R,6S)-6-(3-cyclopentylpropoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-ethyl]-acetamide trifluoroacetate

Dissolve (2S,5R)-5-[(1S,2S)-2-Acetylamino-1-benzoyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3-cyclopentylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (67 mg,

-66-

0.106 mmol) in neat trifluoroacetic acid under nitrogen. After 20 min, dilute the reaction mixture with dichloromethane and concentrate it on the rotary evaporator four times, then dilute with benzene and concentrate again. Dry the residue under vacuum to give the title compound.

5 MS (ES⁺): 531.2 m/z = [M+H]

Preparation 166

(2S,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

10 [(R)-2-(tert-butyl-dimethylsilanyloxy)-1-(1-ethoxy-2-iodoethoxymethyl)-ethyl]-carbamic acid tert-butyl ester

Dissolve [(R)-1-(tert-butyl-dimethylsilanyloxymethyl)-2-hydroxyethyl]-carbamic acid tert-butyl ester (1.0 g, 3.27 mmol) and ethyl vinyl ether (0.20 g, 2.73 mmol) in acetonitrile (20 mL) and add N-iodosuccinimide (0.735 g, 3.27 mmol). Stir at room
15 temperature 72 hours and pour into saturated aqueous sodium chloride. Extract with ethyl acetate, wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate. Purify (silica gel chromatography, eluting with 100:0 to 10:90 hexanes:ethyl acetate) to give the desired compound (462 mg, 34%).

MS (ES): m/z = 504.4 = [M+H]

20

(2S,5R)-5-(tert-butyl dimethylsilanyloxymethyl)-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

Add sodium hydride (0.044 g, 1.10 mmol, 60% dispersion in mineral oil) to [2-(R)-(tert-butyl-dimethylsilanyloxy)-1-(1-ethoxy-2-iodoethoxymethyl)-ethyl]-carbamic
25 acid tert-butyl ester (0.462 g, 0.918 mmol) in N,N-dimethylformamide (9 mL) at room temperature. Heat to ~50 °C for 4 hours, cool to room temperature and pour into ethyl acetate. Wash with water, 1 N lithium chloride, and saturated aqueous sodium chloride. Dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 100:0 to 1:1 hexanes:ethyl acetate) to give a mixture of two diastereomers, the more polar
30 of which is the desired compound.

¹H-NMR (400 MHz, CDCl₃) δ 4.69 (br s, 1H), 3.98-3.45 (m, 8H), 3.07 (d, J = 12.8 Hz, 1H), 1.46 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

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(2S,5S)-2-Ethoxy-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve (2S,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.39 g, 1.04 mmole) in tetrahydrofuran (3 mL) and add
5 tetrabutylammonium fluoride (2.1 mL, 2.1 mmol, 1.0 M in tetrahydrofuran). Stir 45 minutes at room temperature, concentrate and purify (silica gel chromatography, eluting with 10:90 to 40:60 ethyl acetate:hexanes) to give the desired compound (252 mg, 92%).
¹H-NMR (400 MHz, CDCl₃) δ 4.69 (br s, 1H), 4.08-4.04 (m, 2H), 3.88-3.66 (m, 4H), 3.56 (d, J = 10.8 Hz, 1H), 3.51-3.43 (m, 1H), 3.20 (d, J = 14Hz, 1H), 1.47 (s, 9H), 1.22 (t,
10 J = 7.2 Hz, 3H).

(2S,5R)-5-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

Add pyridine sulfur trioxide complex (0.283 g, 1.78 mmol) in dimethylsulfoxide
15 (1.5 mL) to a solution of (2S,5S)-2-ethoxy-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (0.245 g, 0.938 mmol) and triethylamine (0.180 g, 1.78 mmol) in dimethylsulfoxide (3 mL) at room temperature. Stir at room temperature for 4 hours and pour into 50 mL of 10:90 ethyl acetate:hexanes. Wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate. Dissolve the residue in
20 tetrahydrofuran (1.5 mL) and add 3,5-difluorophenyl nitroethane (0.134 g, 0.725 mmol). Cool in an ice water bath and add tetrabutyl ammonium fluoride (0.70 mL, 0.70 mmol, 1.0 M in tetrahydrofuran) all at once. Stir 30 minutes and pour into cold water containing saturated aqueous sodium chloride (~20 mL). Extract with ethyl acetate, wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), concentrate and purify
25 (silica gel chromatography, eluting with 100:0 to 70:30 hexanes:ethyl acetate) to give the desired compound (159 mg, 54%).
MS (ES): $m/z = 445.2 = [M-H]$

(2S,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester
30

Add sodium borohydride (0.061 g, 1.62 mmol) portionwise to a solution of
(2S,5R)-5-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2-

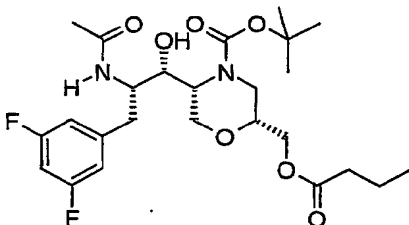
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ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.145 g, 0.325 mmol) and nickel (II) chloride (0.063 g, 0.487 mmol) at room temperature in methanol (5 mL) and stir 30 for min. Add water (~3 mL) and concentrate. Dilute with ethyl acetate and filter through a filtering agent. Partition the filtrate between ethyl acetate and water, dry (magnesium sulfate) and concentrate to give the title compound as a white solid (95 mg, 70%).

MS (ES): $m/z = 417.3 = [M+H]$

Preparation 167

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-butyryloxymethylmorpholine-4-carboxylic acid tert-butyl ester



(R)-4-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Add sodium hydride (2.26 g, 56.47 mmol) and benzyl bromide (10.53 g, 61.60 mmol) to (R)-4-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (3.97 g, 10.27 mmol) in N,N-dimethylformamide (100 mL) at room temperature. Heat to 85 °C for 14 hours. Cool to room temperature and pour into ethyl acetate. Wash with water, 1 N lithium chloride and saturated aqueous sodium chloride. Concentrate and purify (silica gel chromatography, eluting with 5:95 to 10:90 diethyl ether:hexanes) to give the desired compound (2.42 g, 36%).

MS (ES): $m/z = 658 = [M+H]^+$

(2R,3R,4S)-2-Amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol

Dissolve 4-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (2.42 g, 3.68 mmol) in dry dioxane (16 mL). To the solution add 4 M hydrogen chloride in 1,4-dioxane (32.2

-69-

mL, 129 mmol) and stir for three hours. Concentrate to give the hydrochloride salt of the desired product as a white solid (2.17 g, 100%). Slurry the solid in ethyl acetate (150 mL) and stir vigorously with saturated sodium bicarbonate (100 mL). Separate the layers and dry (magnesium sulfate) to give the desired compound.

5 MS (ES): $m/z = 517 [M+H]^+$

Butyric acid (R)-3-[(1R,2R,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethylbutylamino]-2-hydroxypropyl ester

Slurry the (2R,3R,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (1.17 g, 2.26 mmol) in ethanol (11.5 mL) in a sealed tube flushed with nitrogen. Add butyric acid (R)-1-oxiranylmethyl ester (0.96 mL, 6.79 mmol), seal the tube and heat at 85 °C for three hours. Concentrate and purify (silica gel chromatography, eluting with 1.25% to 3.75% [2 M ammonia in methanol]/dichloromethane) to give the desired compound as a mixture of isomers as a white foam

10
15 (1.07 g, 71%).

MS (ES): $m/z = 662 [M+H]^+$

Butyric acid (R)-3-[(1R,2S,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethyl-butyl]-tert-butoxycarbonyl-amino}-2-hydroxypropyl ester

Dissolve the butyric acid (R)-3-[(1R,2R,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethyl-butylamino]-2-hydroxypropyl ester mixture (1.06 g, 1.62 mmol) in dry tetrahydrofuran (tetrahydrofuran) (2.5 mL). Add diisopropylethyl amine (0.57 mL, 3.24 mmol) and di-tert-butyl dicarbonate (587 mg, 2.69 mmol) and stir for 3.5 days. Add water (60 mL) and extract the mixture with ethyl acetate (100 mL).

20
25 Wash the organic layer (60 mL) with water and saturated aqueous sodium chloride (50 mL), dry (magnesium sulfate) and purify (silica gel chromatography, eluting with 25:75 to 45:65 ethyl acetate:hexanes) to give the desired compound as a white foam (479 mg, 39%).

MS (ES): $m/z = 762 [M+H]^+$

30

(2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-butyryloxymethylmorpholine-4-carboxylic acid tert-butyl ester

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Dissolve in a round bottom flask charged with argon butyric acid (R)-3-
{[(1R,2S,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-
hydroxymethylbutyl]-tert-butoxycarbonyl-amino}-2-hydroxy-propyl ester (367 mg, 0.483
mmol) in dry benzene (4.5 mL). Add tributylphosphine (0.180 mL, 0.724 mmol)
5 followed by the addition of tetramethylazodicarboxamide (125 mg, 0.724 mmol).
Vigorously stir the resulting slurry overnight. Concentrate and purify (silica gel
chromatography, eluting with 15:85 to 20:80 diether ether:hexanes) to give the desired
compound as a white foam (302 mg, 84%).

MS (ES): $m/z = 744$ $[M+H]^+$

10
(2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-
butyryloxymethyl-morpholine-4-carboxylic acid tert-butyl ester

Dissolve (2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-
difluorophenyl)-propyl]-2-butyryloxymethyl-morpholine-4-carboxylic acid tert-butyl
15 ester (295 mg, 0.397 mmol) in ethanol (29 mL). Add 20% palladium hydroxide on
carbon (330 mg) and stir under 1 atmosphere of hydrogen gas for 48 hours. Filter
through a filtering agent and wash with ethanol. Concentrate the filtrate to give the
desired compound as a white foam (188 mg, 100%).

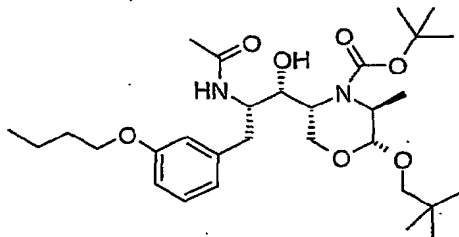
MS(ESI): $m/z = 473$ $[M+H]^+$

20
Amide Formation

To (R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-
butyryloxymethyl-morpholine-4-carboxylic acid tert-butyl ester (0.187 g, 0.396 mmol) in
tetrahydrofuran (4 mL), add triethylamine (0.037 mL, 0.396 mmol) and acetic anhydride
25 (0.055 mL, 0.396 mmol). Stir the solution for 3 hours. Concentrate and purify (silica gel
chromatography, eluting with 50:50 to 60:40 ethyl acetate:hexanes) to give the title
compound as a white foam (125 mg, 61%).

MS (ES): $m/z = 415$ $[M-100+H]^+$

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(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(4-butoxyphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine 4-carboxylic acid tert-butyl ester
3-(1-Hydroxy-2-nitroethyl)-phenol

- 5 Dissolve 3-hydroxybenzaldehyde (18.4 g, 15.07 mmol) in tetrahydrofuran (100 mL). Add nitromethane ((42 mL, 780 mmol), cool in an ice bath and add tetrabutylammonium fluoride (151 mL, 151 mmol, 1.0 M in tetrahydrofuran). Stir for 2 hours, dilute with ethyl acetate (200 mL), wash with water (3 x 500 mL) and saturated aqueous sodium chloride (200 mL). Extract the aqueous washes with diethyl ether (3x),
10 wash with saturated aqueous sodium chloride, dry (magnesium sulfate), filter through a pad of silica gel, and concentrate. Suspend the residue in hot dichloromethane with ~5% ethyl acetate, cool and filter solid. Purify filtrate using silica gel chromatography, eluting with 5:95 ethyl acetate:dichloromethane. Combine the solid from the dichloromethane trituration with the purified filtrate to give the desired compound (24.88 g, 90% total
15 yield).
¹H-NMR (400 MHz, CDCl₃) δ 3.155 (bs, 2H); 4.50 (m, 2H); 5.340 (dd, 1H); 6.777 (m, 1H); 6.845 (m, 2H); 7.201 (t, 1H)

Acetic acid 3-(2-nitrovinyl)-phenyl ester

- 20 Add 3-(1-hydroxy-2-nitroethyl)-phenol (22.3 g, 121.8 mmol), 18-Crown-6 (3.3 g, 12.5 mmol), potassium fluoride (spray-dried) (7.1 g, 141 mmol) to acetic anhydride (115 mL, 1.218 mol). Stir for 1 hour. Cool in an ice bath and pour into ice water (400 mL) and stir for 15 minutes. Decant and extract the aqueous with ethyl acetate (twice). Combine extracts with the solid, wash with water (twice), saturated aqueous sodium
25 chloride (twice), dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 25:75 hexanes:dichloromethane to 100% dichloromethane) to give the desired compound as an orange oil (25.56 g, 91%).

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Acetic acid 3-(2-nitroethyl)-phenyl ester

Dissolve acetic acid 3-(2-nitrovinyl)-phenyl ester (25.56 g, 123.38 mmol) in chloroform (1575 mL). Add silica gel (247 g, 2g/mmol) and isopropanol (370 mL) with
5 mechanical stirring. Add portionwise sodium borohydride (18.67 g, 493.5 mmol) over 10 minutes. Stir at room temperature for 1 hour. Quench with 1 N hydrochloric acid (130 mL) over 20 minutes and stir at room temperature for 15 minutes. Filter solid and wash with dichloromethane (800 mL). Wash filtrate with saturated aqueous sodium chloride (300 mL), dry (magnesium sulfate), filter and concentrate to give the crude phenol
10 intermediate contaminated with reduced starting material which is used directly in the next step. Dissolve the crude intermediate (23.14 g, ~110 mmol) in pyridine (75 mL), cool in an ice bath and add acetic anhydride (4.1 mL, 44 mmol). Stir for 1 hour. Concentrate at ~20 °C, dissolve in ethyl acetate (150 mL), wash with cool 1 N hydrochloric acid (4 x 200 mL), saturated aqueous sodium chloride and dry (magnesium
15 sulfate) and concentrate. Extract the aqueous washes with ethyl acetate, dry (magnesium sulfate) and concentrate. Combine both lots to give the desired compound as an orange oil (25.55 g, 99% total yield).

20 4-(R)-[3-(3-Acetoxyphenyl)-1-(R)-hydroxy-2-(S)-nitropropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Dissolve acetic acid 3-(2-nitroethyl)-phenyl ester (25.53 g, 121.6 mmol) and tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (Gardner's aldehyde) (22.38 g, 97.61 mmol) in dry tetrahydrofuran (200 mL). Cool in ice bath and add tetrabutylammonium fluoride (98 mL, 98 mmol, 1.0 M in tetrahydrofuran) and stir for 15
25 minutes. Pour into ice water (2.7 L), wash with 1 N hydrochloric acid (200 mL), saturated aqueous sodium chloride, dry (magnesium sulfate), filter through a pad of silica gel and concentrate. Purify using silica gel chromatography, eluting with 5:95 ethyl acetate:dichloromethane, followed by 2 separate crystallizations using hexanes/dichloromethane to give the desired compound (18.372 g, 43% total yield).
30 MS(ES): m/z = 437 [M-H]

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4-(R)-[2-(S)-Amino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Add nickel (II) chloride (6.0 g, 46.1 mmol) to a solution of 4-(R)-[3-(3-acetoxyphe-
nyl)-1-(R)-hydroxy-2-(S)-nitropropyl]-2,2-dimethyloxazolidine-3-carboxylic
5 acid tert-butyl ester (18.37 g, 41.9 mmol) in dry methanol (900 mL). Cool in an ice bath
and portionwise sodium borohydride (6.34 g, 167.6 mmol) over 8 minutes. Stir for 10
minutes. And concentrate. Partition the residue between ethyl acetate (200 mL) and
water (200 mL), filter through Celite® and wash with ethyl acetate. Wash the organic
layer with saturated aqueous sodium chloride, combine aqueous washes and extract with
10 ethyl acetate. Combine the organic layers, dry (magnesium sulfate), filter and concentrate
to give the desired compound as a crude foam. Suspend the Celite® cake in ethyl acetate,
filter, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), filter and
concentrate to obtain more desired compound.

MS(ES): $m/z = 367$ [M+H]

15

4-(R)-[1-(S)-benzyloxy-3-(3-benzyloxyphenyl)-2-(S)-dibenzylaminopropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Add tricaprylmethylammonium chloride (Aliquat® 336) (4.5 g, 11.2 mmol) and
tetrabutylammonium bromide (TBAB) (5.7 g, 15.7 mmol) to a solution of 4-(R)-[2-(S)-
20 amino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic
acid tert-butyl ester (16.45 g, crude) in tetrahydrofuran (200 mL). Add portionwise 95%
sodium hydride (2.6 g, 90 mmol) and stir for 10 minutes. Add benzyl bromide (13.4 mL,
112.5 mmol) and heat at 60 °C for 40 minutes and concentrate. Add more 95% sodium
hydride (5.4 g, 225 mmol) and benzyl bromide (27 mL, 225 mmol) in tetrahydrofuran (~5
25 mL) and stir overnight at 65 °C. Dilute with ethyl acetate, quench with water (300 mL),
wash with water, and saturated aqueous sodium chloride. Extract the aqueous washes
with ethyl acetate, combine the organic layers, dry (magnesium sulfate), filter and purify
twice (silica gel chromatography, eluting with 5:95 to 10:90 ethyl acetate:hexanes) to
give the desired compound as an orange residue (16.01 g, 49%).

30 MS(ES): $m/z = 727$ [M+H]

2-(R)-Amino-3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-4-(S)-dibenzylaminopentan-1-ol

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Dissolve 4-(R)-[1-(S)-benzyloxy-3-(3-benzyloxyphenyl)-2-(S)-dibenzylaminopropyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (16.01 g, 22.0 mmol) in 4 M hydrogen chloride in 1,4-dioxane (130 mL) and stir for 30 minutes. Add water (65 mL) and stir for 18 hours. Slowly add sodium bicarbonate (50 g) and water (~50 mL). Extract with ethyl acetate, wash with saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate to give the crude desired compound.

MS(ES): m/z = 587 [M+H]

- 10 3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-2-[2,2-bis-(2,2-dimethylpropoxy)-1-(S)-methyl-ethylamino]-4-(S)-dibenzylaminopentan-1-(R)-ol
3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-2-[2,2-bis-(2,2-dimethylpropoxy)-1-(R)-methyl-ethylamino]-4-(S)-dibenzylaminopentan-1-(R)-ol

- Add 3 Å molecular sieves (3.4 g, 0.155 g/mmol) to a solution of 2-(R)-amino-3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-4-(S)-dibenzylaminopentan-1-ol (12.75 g, 21.73 mmol), 1,1-bis-(2,2-dimethylpropoxy)-propan-2-one (9.3 mL, 34.77 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (0.545 g, 2.17 mmol) in dry toluene (100 mL) under nitrogen. Reflux in a Dean Stark trap for 18 hours. Cool, filter and dissolve the solid in dry methanol (150 mL). Cool in an ice bath and add sodium cyanoborohydride (5.5 g, 86.92 mmol), followed by the slow addition of glacial acetic acid (2.5 mL, 43.5 mmol) and stir 2.5 hours. Sonicate the reaction to increase solubility. Filter, wash with methanol, and add water (15 mL), 2 N sodium hydroxide (100 mL) and ethyl acetate (100 mL) and stir for 10 minutes. Add saturated aqueous sodium chloride and wash the organic layer with 2 N sodium hydroxide (2 x 100 mL) and saturated aqueous sodium chloride. Extract the aqueous washes with ethyl acetate, wash with saturated aqueous sodium chloride, combine organic layers, dry (magnesium sulfate), filter and concentrate. Separate the two isomers using silica gel chromatography, eluting with hexanes/dichloromethane to give the two desired compounds 3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-2-[2,2-bis-(2,2-dimethylpropoxy)-1-(S)-methyl-ethylamino]-4-(S)-dibenzylaminopentan-1-(R)-ol (2.911 g, 17%) and 3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-2-[2,2-bis-(2,2-dimethylpropoxy)-1-(R)-methyl-ethylamino]-4-(S)-dibenzylaminopentan-1-(R)-ol (2.167 g, 12%).

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(S)-Dibenzyl-{2-(R)-benzyloxy-1-(3-benzyloxybenzyl)-2-(R)-[6-(R)-(2,2-dimethylpropoxy)-5-(R)-methylmorpholin-3-yl]-ethyl}-amine

- 5 Add dropwise boron trifluoride diethyl etherate (1.4 mL, 10.89 mmol) to a solution of 3-(R)-benzyloxy-5-(3-benzyloxyphenyl)-2-[2,2-bis-(2,2-dimethylpropoxy)-1-(S)-methyl-ethylamino]-4-(S)-dibenzylaminopentan-1-(R)-ol (2.91 g, 3.63 mmol) in 1,2-dichloroethane (40 mL) and heat at 100 °C for 10 minutes. Dilute with dichloromethane, wash with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 15:85 ethyl acetate:hexanes) to give the desired compound (1.806 g, 70%).

MS (ES): m/z = 713 [M+H]

5-(R)-[1-(S)-benzyloxy-3-(3-benzyloxyphenyl)-2-(R)-dibenzylaminopropyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester

- 15 Add N,N-diisopropylethylamine (813 μ L, 4.67 mmol) to a solution of (S)-dibenzyl-{2-(R)-benzyloxy-1-(3-benzyloxybenzyl)-2-(R)-[6-(R)-(2,2-dimethylpropoxy)-5-(R)-methylmorpholin-3-yl]-ethyl}-amine (1.664 g, 2.335 mmol) and di-tert-butyl dicarbonate (1.53 g, 7.0 mmol) in dry 1,2-dichloroethane (20 mL) and heat to 70 °C for 18 hours. Wash with 1 N hydrochloric acid, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 5:95 to 10:90 ethyl acetate:hexanes) to give the desired compound as a white foam (1.38 g, 73%).

MS (ES): m/z = 813 [M+H]

- 25 5-(R)-[2-(S)-Amino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester

- Dissolve 5-(R)-[1-(S)-benzyloxy-3-(3-benzyloxyphenyl)-2-(R)-dibenzylaminopropyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester (1.38 g, 1.70 mmol) in tert-butanol (~50 mL). Add 20% palladium hydroxide on carbon (4 g) and hydrogenate at 50 psi hydrogen gas at 40 °C for 30 18 hours. Filter and concentrate to give the desired compound (802 mg).

MS (ES): m/z = 453 [M+H]

5-[2-(S)-Acetylamino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester

Add acetic anhydride (320 μ L, 3.4 mmol) and N,N-diisopropylethylamine (590 μ L, 3.4 mmol) to a solution of 5-(R)-[2-(S)-amino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester (770 mg, 1.70 mmol). Stir for 2.5 hours. Dilute with ethyl acetate, wash with 1 N hydrochloric acid (twice), saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 20:80 to 25:75 ethyl acetate:hexanes) to give the desired compound (292 mg).

MS (ES): m/z = 495 [M+H]

5-(R)-[2-(S)-Acetylamino-3-(3-butoxyphenyl)-1-(S)-hydroxypropyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester

Add 1-bromobutane (6 μ L, 55.6 μ mol) to a solution of 5-[2-(S)-acetylamino-1-(S)-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid tert-butyl ester (25 mg, 50.5 μ mol) and cesium carbonate (33 mg, 1.01 μ mol) in N,N-dimethylformamide (250 μ L). Heat to 60 $^{\circ}$ C for 3 hours. Dilute with ethyl acetate, wash with water, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 20:80 to 85:15 ethyl acetate:dichloromethane) to give the title compound (28.5 mg, 80%).

MS (ES): m/z = 573 [M+Na]

The compounds of Preparations 169-183 may be prepared essentially as described in Preparation 168 using the appropriate alkyl bromides.

| Prep | Compound | MS (ES) [M+Na] |
|------|--|-------------------|
| 169 | 5-(R)-{2-(S)-Acetylamino-1-(S)-hydroxy-3-[4-(3-methylbutoxy)-phenyl]-propyl}-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 587 |
| 170 | 5-(R)-[2-(S)-Acetylamino-1-(S)-hydroxy-3-(3-propoxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 559 |
| 171 | 5-(R)-[2-(S)-Acetylamino-1-(S)-hydroxy-3-(3-isobutoxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine-4- | 573 |

| | | |
|------|--|----------------------------|
| | carboxylic acid <u>tert</u> -butyl ester | |
| 172 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2-fluoro-ethoxy)-phenyl]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 563 |
| 173 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2,2-difluoro-ethoxy)-phenyl]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 581 |
| 174 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-[3-(2-methyl-butoxy)-phenyl]-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 587 |
| 175 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-propoxy-phenyl)-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 439 [M-t-Bu+H] |
| 176 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-hydroxy-phenyl)-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 559 |
| 177 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-cyclopentylmethoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 599 |
| 178 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-[3-((S)-2-methyl-butoxy)-phenyl]-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 587 |
| 179 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-ethoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 545 |
| 180 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-allyloxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 557 |
| 181* | (2R,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.3 [M ⁺] |
| 182* | (2R,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-isobutoxy-5-fluorophenyl)-propyl]-2-(cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 581.3 [M ⁺] |
| 183* | (2R,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(2,2,2-trifluoroethoxy-5-fluorophenyl)-propyl]-2-(cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 607.3 [M ⁺] |

*Prepared as described in Preparation 168 beginning with 5-(R)-[1-(S)-benzyloxy-3-(3-benzyloxyphenyl)-2-(R)-dibenzylaminopropyl]-2-(R)-(cyclohexylmethoxy)-lmorpholine-4-carboxylic acid tert-butyl ester

Preparation 184

- 5 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

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5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

Toluene-4-sulfonic acid 2-(S)-hydroxy-5-methylhexyl ester

Add dropwise over 5 minutes isobutylmagnesium bromide (4.4 mL, 8.8 mmol, 2 M in diethyl ether) to a solution of lithium tetrachlorocuprate (4.4 mL, 0.44 mmol, 0.1 M in tetrahydrofuran) cooled to -35-40 °C. Dissolve (2S)-(+)-glycidyl tosylate (1.674 g, 7.73 mmol) in tetrahydrofuran (8 mL), cool to -40 °C and cannulate into the stirring Grignard reaction flask. Quench with saturated aqueous ammonium chloride (25 mL), pour supernate into saturated aqueous ammonium chloride (25 mL) and water and shake well. Wash with saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 10:90 to 25:75 ethyl acetate:hexanes) to give the desired compound (1.6711 g, 75%).

15 1-[2-(R)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethylbutylamino]-5-methylhexan-2-(S)-ol

Add potassium carbonate (555 mg, 4.013 mmol) to a solution of 2-amino-3-(R)-benzyloxy-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-(R)-ol (1.0366 g, 2.06 mmol) and toluene-4-sulfonic acid 2-(S)-hydroxy-5-methylhexyl ester (1.037 g, 2.006 mmol) in dry methanol (4.5 mL). Heat at 80 °C in a sealed vessel for 48 hours. Partition between ethyl acetate and water, wash with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 20:80 to 50:50 ethyl acetate:hexanes) to give the desired compound (672 mg, 53%).

MS (ES): m/z = 631 [M+H]

25

[2-(S)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethylbutyl]-(2-(S)-hydroxy-5-methylhexyl)-carbamic acid tert-butyl ester

Dissolve 1-[2-(R)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethylbutylamino]-5-methylhexan-2-(S)-ol (672 mg, 1.06 mmol) in dichloromethane (10 mL). Add 20% aqueous sodium carbonate (10 mL), hydroxylamine (6.5 μ L, 0.106 mmol, 50 wt %) and then di-tert-butyl dicarbonate (0.236 g, 1.06 mmol) and stir 72 hours. Separate layers, extract with dichloromethane, dry (magnesium sulfate),

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filter and concentrate. Dissolve in methanol and add more di-tert-butyl dicarbonate (0.480 g, 2.2 mmol) and stir at room temperature over the weekend. Concentrate and purify on silica gel, eluting with 10:90 to 25:75 ethyl acetate:hexanes to give the desired compound (292 mg).

5

5-(R)-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

Dissolve [2-(S)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethylbutyl]-(2-(S)-hydroxy-5-methylhexyl)-carbamic acid tert-butyl ester (253 mg, 347 μ mol) in benzene (3 mL). Deoxygenate the reaction mixture. Add tributyl phosphine (130 μ L, 520 mmol), N,N-tetramethyl azodicarboxamide (TMAD) (89.5 mg, 520 mmol) and stir at room temperature 2.5 hours. Add deoxygenated tetrahydrofuran (5 mL), more tributyl phosphate (130 μ L), more TMAD (90 mg) and stir 1.5 hours. Filter, rinse with hexanes, concentrate and purify (silica gel chromatography, eluting with 5:95 ethyl acetate:hexanes) to give the desired compound (191.7 mg, 77%).
MS (ES): m/z = 713 [M+H]

5-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

Dissolve 5-(R)-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester (187.7 mg, 0.263 mmol) in methanol (10 mL). Add 20% palladium hydroxide on carbon (100 mg) and hydrogenate at one atmosphere hydrogen gas for 18 hours. Add more 20% palladium hydroxide on carbon (100 mg) and further hydrogenate at one atmosphere hydrogen gas for 5 hours. Filter and concentrate to give the desired compound (107.8 mg, 93%).
MS (ES): m/z = 443 [M+H]

5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester

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Add acetic anhydride (25 μ L, 0.264 mmol) to a solution of 5-(R)-[2-(S)-amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester (107 mg, 0.240 mmol) and triethylamine (37 μ L, 0.267 mmol) in tetrahydrofuran (5 mL) and stir at room temperature for 18 hours. Concentrate and purify (silica gel chromatography, eluting with 80:20 ethyl acetate:dichloromethane), to separate the two title compounds 5-(R)-[2-(S)-acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester (0.141 g, 59%) and 5-(S)-[2-(R)-acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine-4-carboxylic acid tert-butyl ester (25.1 mg, 22%).

MS (ES): m/z = 507 [M+Na]

The compounds of Preparations 185-186 may be prepared essentially as described in Preparation 184 using neopentylmagnesium bromide and 3,3-dimethylbutane-magnesium bromide (Org Synth, 68, 104, (1989)) respectively.

| Prep | Compound | MS (ES) [M+H] |
|------|--|------------------|
| 185 | 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3,3-dimethylbutyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester 5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3,3-dimethylbutyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 727 |
| 186 | 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(4,4-dimethylpentyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester 5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(4,4-dimethylpentyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 741 |

Preparation 187

(S)-Dibenzyl-[2-(4-(R)-benzylmorpholin-3-yl)-2-(S)-benzyloxy-1-(3,5-difluorobenzyl)-ethyl]-amine

20 3-benzylamino-4-(R)-benzyloxy-5-(S)-dibenzylamino-6-(3,5-difluorophenyl)-hexan-1-(R)-ol

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Add magnesium sulfate (2.5 g), 4Å molecular sieves (2.5 g) followed by benzaldehyde (0.95 mL, 9.35 mmol) to a solution of 2-amino-3-(R)-benzyloxy-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-(R)-ol (4.60 g, 8.90 mmol) in dry tetrahydrofuran (5 mL). Stir at room temperature for 1.5 hours, filter and concentrate.

- 5 Dissolve the residue in absolute ethanol (5 mL), cool in an ice bath and add sodium borohydride in 3 portions (330 mg, 8.9 mmol). Remove ice bath and stir at room temperature overnight. Add 1 N hydrochloric acid (3 mL) and stir for 5 minutes. Pour into a separatory funnel containing dichloromethane/water and basify to about pH = 10 using saturated aqueous potassium carbonate (~20 mL). Extract with dichloromethane (2
10 x 150 mL), dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 30:70 to 40:60 ethyl acetate:hexanes) to give the desired compound as a light yellow oil (3.93 g, 73%).
MS (ES) = 607.2 [M+H]

- 15 4-benzyl-5-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(R)-(3,5-difluorophenyl)-propyl]-morpholin-3-one

- Dissolve 3-benzylamino-4-(R)-benzyloxy-5-(S)-dibenzylamino-6-(3,5-difluorophenyl)-hexan-1-(R)-ol (0.673 g, 1.11 mmol) in toluene (5 mL), cool to 0 °C and add triethylamine (0.15 mL, 1.11 mmol). Add slowly chloroacetyl chloride (0.09 mL,
20 1.11 mmol). Stir at 0 °C for 1 hour and at room temperature overnight (JCS Perk Trans 1, 1987, 547). Wash with saturated aqueous sodium chloride (30 mL), dry (sodium sulfate), filter and concentrate. Dissolve in *tert*-butanol, add potassium *tert*-butoxide and heat to reflux for 6 hours. Concentrate, dissolve in ethyl acetate, wash with 1 N hydrochloric acid, saturated aqueous sodium chloride, dry (sodium sulfate), filter and purify (silica gel
25 chromatography, eluting with 30:70 ethyl acetate:hexanes) to give the desired compound as a white foam (0.375 g, 52%).
MS (ES) = 647.2 [M+H]

- 30 (S)-Dibenzyl-[2-(4-(R)-benzylmorpholin-3-yl)-2-(S)-benzyloxy-1-(3,5-difluorobenzyl)-ethyl]-amine

Dissolve 4-benzyl-5-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(R)-(3,5-difluorophenyl)-propyl]-morpholin-3-one (0.308 g, 0.476 mmol) in dry tetrahydrofuran (3

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mL) under nitrogen and cool to 0 °C. Add borane-methyl sulfide complex (1 mL, 2 mmol, 2 M in tetrahydrofuran) and let stir over the weekend (JCS Perkins Trans., 1, 1987, 547). Add 8 drops of water and concentrate. Dissolve in ethyl acetate and wash with water, 0.1 N sodium hydroxide, dry (sodium sulfate), filter and purify (silica gel chromatography, eluting with 20:80 ethyl acetate: hexanes) to give the title compound as a white foam (0.143 g, 48%).

MS (ES) = 633.3 [M+H]

Preparation 188

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-chloro-5-fluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester
(2R,5R)-2-(2,2-Dimethylpropoxy)-5-formylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve (2R,5S)-2-(2,2-dimethylpropoxy)-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (3.67 g, 12.1 mmol) in anhydrous dimethylsulfoxide (25 mL) and dichloromethane (4 mL) and cool to 0 °C under nitrogen. Add diisopropylethylamine (7.4 mL, 42.3 mmol) then pyridine sulfur trioxide (3.47 g, 21.8 mmol) in 2 portions. Stir at 0 °C for 20 minutes and then remove from the cooling bath to allow all solids to dissolve. Pour into ice cold saturated aqueous sodium chloride, extract with 10% ethyl acetate/hexanes, wash with 0.1 N aqueous citric acid (30 mL), saturated aqueous sodium chloride (30 mL), dry (magnesium sulfate), filter and concentrate to give the desired compound as a colorless oil (3.37 g, 92%).

1-Chloro-3-fluoro-5-(E)-2-nitrovinyl)-benzene

Dissolve 3-chloro-5-fluorobenzaldehyde (4.0 g, 25.2 mmol) in glacial acetic acid (15 mL). Add nitromethane (4.1 mL, 75.7 mmol) and ammonium acetate (1.94 g, 25.2 mmol) and heat to reflux for 4 hours. Cool and pour over ice. Dilute with 2 N sodium hydroxide and extract with ethyl acetate, dry (magnesium sulfate), concentrate and purify (silica gel chromatography, eluting with 1:1 dichloromethane:hexanes) to give the desired compound as a beige solid (2.97 g, 58%).

1-Chloro-3-fluoro-5-(2-nitroethyl)-benzene

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Add sodium borohydride (0.75 g, 19.7 mmol) to a solution of 1,4-dioxane (10 mL) and absolute ethanol (2.5 mL) in a room temperature water bath. Next add 1-chloro-3-fluoro-5-((E)-2-nitrovinyl)-benzene (1.5 g, 8.98 mmol) in 1,4-dioxane (10 mL) dropwise and stir at room temperature for 1 hour (Bhattacharjya, Synthesis, 1985, 886-997). Add ice chips, glacial acetic acid (2 mL), water (2 mL), concentrate and dilute in dichloromethane/water. Wash the dichloromethane layer with water, saturated aqueous sodium chloride, dry (sodium sulfate), filter and purify (silica gel chromatography, eluting with 1:1 dichloromethane:hexanes) to give the desired compound as an oil (1.07 g 70%).

¹H NMR (CDCl₃) δ 3.30 (t, 2H, J = 8Hz), 4.62 (t, 2H, J = 8Hz), 6.85 (m, 1H), 7.02 (m, 2H)

(2R,5R)-5-[(1R,2S)-3-(3-Chloro-5-fluorophenyl)-1-hydroxy-2-nitropropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add 1-chloro-3-fluoro-5-(2-nitroethyl)-benzene (0.343 g, 1.68 mmol) in dry tetrahydrofuran (2 mL) to a solution of (2R,5R)-2-(2,2-dimethylpropoxy)-5-formylmorpholine-4-carboxylic acid tert-butyl ester (0.462 g, 1.53 mmol) in tetrahydrofuran (7 mL). Add tetrabutylammonium fluoride (0.77 mL, 0.765 mmol, 1.0 M in tetrahydrofuran) and stir at room temperature for 1 hour. Dilute with ethyl acetate and wash with saturated aqueous sodium chloride, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 2:98 ethyl acetate:dichloromethane) to give the desired compound as a white foam (0.455 g, 59%).

MS (ES): *m/z* = 503.3 [M-H]

(2R,5R)-5-[(1S,2S)-2-Amino-3-(3-chloro-5-fluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Dissolve (2R,5R)-5-[(1R,2S)-3-(3-chloro-5-fluorophenyl)-1-hydroxy-2-nitropropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.455 g, 0.901 mmol) in methanol (8 mL) and stir at room temperature in an oil bath. Add anhydrous nickel (II) chloride (0.175 g, 1.35 mmol) followed by sodium borohydride (0.170 mg, 4.50 mmol) in 3 portions over 5 minutes and stir for 15 minutes. Add water (2 mL), 0.1 N sodium hydroxide (2 mL) and extract with ethyl acetate (2 x 30 mL).

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Combine organic extracts, wash with saturated aqueous sodium chloride (30 mL), dry (sodium sulfate), filter through a pad of Celite® and concentrate to give the desired compound as a colorless oil (0.428 g).

MS (ES): $m/z = 475.2$ [M+H]

5

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-chloro-5-fluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add triethylamine (138 μ L, 0.99 mmol) to a solution of (2R,5R)-5-[(1S,2S)-2-amino-3-(3-chloro-5-fluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.428 g, 0.901 mmol) in tetrahydrofuran (5 mL) followed by acetic anhydride (91 μ L, 0.991 mmol). Stir at room temperature for 30 minutes, dilute with dichloromethane, wash with 0.1 N hydrochloric acid (30 mL), saturated aqueous sodium chloride (30 mL), dry (sodium sulfate), filter and purify (silica gel chromatography, eluting with 2:98 to 10:90 methanol:dichloromethane) to give the title compound as a white foam (0.212 g, 45%).

15

MS (ES): $m/z = 539.2$ [M+Na]

The compounds of Preparations 189-202 may be prepared essentially as described in Preparation 188 above using the appropriate benzaldehydes and formylmorpholines.

| Prep | Compound | MS (ES) [M+Na] |
|------|---|-------------------|
| 189 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(2,3,5-trifluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 541.3 |
| 190 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-trifluoromethoxyphenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 571.3 |
| 191 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-trifluoromethylphenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 192 | (2R,5R)-5-[2-Amino-3-(3-benzyloxyphenyl)-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 555 |
| 193 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 503.3 |
| 194 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-dimethylphenyl)-1- | |

| | | |
|-----|--|-------|
| | hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 195 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-isobutylsulfanylphenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 196 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-isobutylsulfanylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 197 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-propylsulfanylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 198 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-propylsulfanylphenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 199 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-butyl-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553.5 |
| 200 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-(2,2,2-trifluoroethoxy)-phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 599.2 |
| 201 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-trifluoromethoxyphenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 202 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-methoxyphenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |

Preparation 203

Toluene-4-sulfonic acid (S)-2-hydroxy-4-phenylbutyl ester

- Add phenyl methyl magnesium bromide (14 mL, 14 mmol, 1 M in tetrahydrofuran) to a solution of lithium tetrachlorocuprate (5.5 mL, 0.55 mmol, 0.1 M in tetrahydrofuran) in dry tetrahydrofuran (10 mL) and stir at -35°C (acetonitrile/dry ice bath) for 15 minutes (J. Med. Chem., **41**, 2451-2460, (1998); JOC, **54**, 1295-1304, (1989)). Cool to -35°C a solution of (2S)-(+)-glycidyl tosylate (2.51 g, 11.0 mmol) in dry tetrahydrofuran (4 mL) and transfer rapidly via cannula to the Grignard solution. Stir for 1 hour at -35°C , quench with a saturated aqueous ammonium chloride solution and dilute with diethyl ether. Wash the organic layer with saturated aqueous sodium chloride, dry (sodium sulfate), concentrate and purify (silica gel chromatography, eluting with 35:65 ethyl acetate:hexanes) to give the desired compound as a colorless oil (1.77 g, 50%) MS (ES): $m/z = 338.3$ [M+18]

The compound of Preparation 204 may be prepared essentially as described in Preparation 203 above using cyclohexylmethylmagnesium bromide.

| Prep | Compound | MS (ES) |
|------|---|-----------------|
| 204 | Toluene-4-sulfonic acid (S)-4-cyclohexyl-2-hydroxybutyl ester | 344.3 [M+18] |

5

Preparation 205

5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

3-(R)-benzyloxy-2-(R)-(4-cyclohexyl-2-(S)-hydroxybutylamino)-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol

- 10 Dissolve 2-(R)-amino-3-(R)-benzyloxy-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (600 mg, 1.16 mmol) and 2-(S)-(2-cyclohexylethyl)-oxirane (179 mg, 1.16 mmol) in absolute ethanol (8 mL) in a sealed glass pressure vessel and heat to 80 °C for 4 days. Concentrate and purify (silica gel chromatography, eluting with 1:99 to 5:95 methanol:dichloromethane) to give the desired compound (510 mg, 65%).
- 15 MS (ES): m/z = 671.5 [M+H]

[2-(S)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethyl-butyl]-(4-cyclohexyl-2-(S)-hydroxy-butyl)-carbamic acid tert-butyl ester

- 20 Add di-tert-butyl dicarbonate (0.19 mL, 0.82 mmol) to a solution of 3-(R)-benzyloxy-2-(R)-(4-cyclohexyl-2-(S)-hydroxybutylamino)-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (424 mg, 0.63 mmol) and diisopropylethylamine (0.19 mL, 1.07 mmol) in tetrahydrofuran. Stir overnight at room temperature and add more di-tert-butyl dicarbonate (0.4 mL). Stir another day, concentrate, dilute with ethyl acetate, wash with dilute aqueous sodium bicarbonate, dry (sodium sulfate), filter, concentrate and
- 25 purify (silica gel chromatography, eluting with 10:90 ethyl acetate:dichloromethane) to give the desired compound (317 mg, 65%).
- MS (ES): m/z = 771.5 [M+H]

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5-(R)-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

Add tri-*n*-butylphosphine (0.20 mL, 0.82 mmol) and 1,1'-azobis(N,N-dimethylformamide) (diamide) (142 mg, 0.82 mmol) to a solution of [2-(S)-benzyloxy-3-(S)-dibenzylamino-4-(3,5-difluorophenyl)-1-(R)-hydroxymethylbutyl]-(4-cyclohexyl-2-(S)-hydroxybutyl)-carbamic acid tert-butyl ester (317 mg, 0.41 mmol) in dry tetrahydrofuran (5 mL) and stir at room temperature for 3 days. Filter, dilute filtrate with ethyl acetate, wash with 0.1 N hydrochloric acid/saturated aqueous sodium chloride (50 mL), dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with dichloromethane to give the desired compound as a white foam (232 mg, 75%).

MS (ES): $m/z = 753.5$ [M+H]

5-(R)-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

Add 20% palladium hydroxide on carbon (Pearlman's catalyst) (232 mg) to a solution of 5-(R)-[1-(S)-benzyloxy-2-(S)-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester (232 mg, 0.31 mmol) in methanol (5 mL). Stir under 1 atmosphere of hydrogen gas at room temperature overnight, filter through a pad of Celite® and concentrate to give the desired compound as a colorless oil which is used directly without further purification (138 mg, 93%).

MS (ES): $m/z = 483.3$ [M+H]

5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

Add triethylamine (0.04 mL, 0.32 mmol) followed by acetic anhydride (0.03 mL, 0.32 mmol) to a solution of 5-(R)-[2-(S)-amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester (138 mg, 0.29 mmol) in dry tetrahydrofuran (3 mL). Stir at room temperature for 10 min. Dilute with dichloromethane, wash with 0.1 N hydrochloric acid (30mL), dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 45:55 to 70:30 ethyl acetate:dichloromethane) to give the title compound (57mg).

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MS (ES): $m/z = 547.2$ [M+Na].

The compound of Preparation 206 may be prepared essentially as described in Preparation 228 using toluene-4-sulfonic acid (S)-2-hydroxy-4-phenylbutyl ester.

| Prep | Compound | MS (ES) |
|------|---|-----------------|
| 205 | (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-phenethylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 541.3 [M+Na] |

5

Preparation 207

5-(R)-(2-(S)-Acetylamino-1-(S)-hydroxy-3-phenylpropyl)-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

1-(1-(R)-benzyloxymethyl-2-hydroxyethylamino)-4-cyclohexylbutan-2-(S)-ol

10 Dissolve (R)-(+)-2-amino-3-benzyloxy-1-propanol (317 mg, 1.75 mmol) and 2-(S)-(2-cyclohexylethyl)-oxirane (270 mg, 1.75 mmol) in absolute ethanol (8 mL) and heat at 80 °C in a sealed glass pressure vessel overnight. Concentrate and purify (silica gel chromatography, eluting with 8:92 to 10:90 methanol:dichloromethane) to give the desired compound (336 mg, 57%).

15 MS (ES): $m/z = 336.2$ [M+H]

(2-(R)-benzyloxy-1-hydroxymethylethyl)-(4-cyclohexyl-2-(S)-hydroxybutyl)-carbamic acid tert-butyl ester

20 Dissolve 1-(1-(R)-benzyloxymethyl-2-hydroxyethylamino)-4-cyclohexylbutan-2-(S)-ol (292 mg, 0.87 mmol) in dry tetrahydrofuran (5 mL) and cool to 0 °C. Add diisopropylethylamine (0.26 mL, 1.48 mmol) followed by di-tert-butyl dicarbonate (0.26 mL, 1.13 mmol) and stir at the same temperature for 3 hours. Remove ice bath and stir 30 minutes. Concentrate, dilute with ethyl acetate, wash with cold 0.1 N hydrochloric acid, dry (sodium sulfate), filter and purify (silica gel chromatography, eluting with
25 2.5:97.5 to 6:94 methanol:dichloromethane) to give the desired compound (325 mg, 86%).

MS (ES): $m/z = 458.3$ [M+Na]

5-(S)-benzyloxymethyl-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

Add tri-*n*-butylphosphine (0.37 mL, 1.49 mmol) and 1,1'-azobis(N,N-dimethylformamide) (diamide) (257 mg, 1.49 mmol) to a solution of (2-(R)-benzyloxy-1-hydroxymethylethyl)-(4-cyclohexyl-2-(S)-hydroxybutyl)-carbamic acid tert-butyl ester
5 (325 mg, 0.75 mmol) in dry tetrahydrofuran (4mL). Stir at room temperature for 3 hours, filter, dilute with ethyl acetate, wash with 0.1 N hydrochloric acid/saturated aqueous sodium chloride (50 mL), dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0.1% to 3:97 methanol:dichloromethane) to give the
10 desired compound as a colorless oil (215 mg, 69%).

MS (ES): m/z = 318.3 (M-BOC)

2-(S)-(2-Cyclohexylethyl)-5-(S)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

15 Add 20% palladium hydroxide on carbon (Pearlman's catalyst) (92 mg) to a solution of 5-(S)-benzyloxymethyl-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester (211 mg, 0.51 mmol) in absolute ethanol (25 mL) and hydrogenate in a Parr shaker at 40 °C for 18 hours at 60 psi. Filter and concentrate to give the desired compound which is used without further purification.

20 MS (ES): m/z = 350.3 [M+Na]

2-(S)-(2-Cyclohexylethyl)-5-(R)-formylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve 2-(S)-(2-cyclohexylethyl)-5-(S)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (165 mg, 0.50 mmol) in dimethylsulfoxide (2 mL), and cool to 10°C.
25 Add triethylamine (0.28 mL, 2.02 mmol) followed by pyridine sulfur trioxide complex and stir for 30min. Dilute with ethyl acetate and pour into cold water. Wash with 5% citric acid (50mL), saturated aqueous sodium chloride (50mL) and dry (sodium sulfate), filter and concentrate give the desired compound as an oil which is used without further purification.

30

2(S)-(2-Cyclohexylethyl)-5-(R)-(1-(R)-hydroxy-2-(S)-nitro-3-phenylpropyl)-morpholine-4-carboxylic acid tert-butyl ester

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Add 1-phenyl-2-nitroethane (91 mg, 0.61 mmol) to a solution of 2-(S)-(2-cyclohexylethyl)-5-(R)-formylmorpholine-4-carboxylic acid tert-butyl ester (164 mg, 0.50 mmol) in dry tetrahydrofuran (6 mL). Cool to 0 °C and add tetrabutylammonium fluoride (0.25 mL of a 1 M solution in tetrahydrofuran, 0.25 mmol) and refrigerate the solution overnight. Dilute with ethyl acetate, wash with cold saturated aqueous sodium chloride (50mL), dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 2.5:97.5 ethyl acetate:dichloromethane) to give the desired compound as a white foam (152 mg, 63%).

MS (ES): m/z = 499.2 [M+Na]

10

5-(R)-(2-(S)-Amino-1-(S)-hydroxy-3-phenylpropyl)-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester

Dissolve 2(S)-(2-cyclohexylethyl)-5-(R)-(1-(R)-hydroxy-2-(S)-nitro-3-phenylpropyl)-morpholine-4-carboxylic acid tert-butyl ester (152 mg, 0.32 mmol) in methanol (5 mL), and place in a room temperature oil bath. Add dry nickel (II) chloride (62 mg, 0.48 mmol) followed by sodium borohydride (30mg, 0.80 mmol). After 3 minutes add a second portion of sodium borohydride (30 mg, 0.80 mmol). Quench with water (1 mL) then 0.1 N sodium hydroxide (3 mL). Dilute with ethyl acetate and extract (3 x 30 mL). Wash the combined extracts with saturated aqueous sodium chloride, filter through a pad of Celite®, dry (sodium sulfate) and concentrate to give the desired compound as a white solid which is used without further purification (140 mg, 99%).

15

20

MS (ES): m/z = 447.5 [M+H]

5-(R)-(2-(S)-Acetylamino-1-(S)-hydroxy-3-phenyl-propyl)-2-(S)-(2-cyclohexyl-ethyl)-morpholine-4-carboxylic acid tert-butyl ester

25

Dissolve 5-(R)-(2-(S)-amino-1-(S)-hydroxy-3-phenylpropyl)-2-(S)-(2-cyclohexylethyl)-morpholine-4-carboxylic acid tert-butyl ester (140 mg, 0.31 mmol) in dry tetrahydrofuran (3 mL). Add triethylamine (0.05mL, 0.35 mmol) followed by acetic anhydride (0.03 mL, 0.35 mmol) and stir at room temperature for 1 hour. Dilute with dichloromethane, wash with 0.1 N hydrochloric acid/saturated aqueous sodium chloride (30mL), dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography,

30

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eluting with 40:60 to 60:40 ethyl acetate:dichloromethane) acetate/dichloromethane to give the title compound (83 mg, 54%).

MS (ES): $m/z = 511.2$ [M+Na]

5

Preparation 208

2-(Ethylmethylcarbamoyl)-cyclopropane carboxylic acid

trans-Cyclopropane-1,2-dicarboxylic acid monoethyl ester

Add a solution of sodium hydroxide pellets (0.501 g, 12.5352 mmol) in methanol (5.22 mL) to a solution of diethyl (E)-cyclopropane-1,2-dicarboxylate (3.00 mL, 16.11 mmol) in acetone (36.9 mL). Stir at room temperature for 24 hours. Acidify the aqueous layer with 5N hydrochloric acid and concentrate. Slurry the residue with ethyl acetate, filter away the sodium chloride and concentrate to give the crude desired compound.

trans-2-(Methylpropylcarbamoyl)-cyclopropane carboxylic acid ethyl ester

15 Add 1-hydroxybenzotriazole (HOBt) (1.46 g, 10.8118 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (2.07 g, 10.8118 mmol) to a solution of crude trans-cyclopropane-1,2-dicarboxylic acid monoethyl ester (1.71g, 10.8118 mmol) in N,N-dimethylformamide (11 mL). Stir for 30 minutes. Add triethylamine (2.26 mL, 16.2177 mmol) and methylpropylamine (1.11 mL, 10.8118 mmol) and stir for 16 hours. Quench with 10% aqueous potassium carbonate (10 mL) and extract with ethyl acetate (3 x 50 mL). Combine the organic extracts, wash with 0.1 N aqueous citric acid (30 mL) and 1 N lithium chloride, dry (magnesium sulfate), concentrate and crystallize with xylenes to give the desired compound (1.02 g, 50%).

25 trans-2-(Methylpropylcarbamoyl)-cyclopropane carboxylic acid

Add 1 N lithium hydroxide (25.6 mL, 25.59 mmol) to a solution of trans-2-(methylpropylcarbamoyl)-cyclopropane carboxylic acid ethyl ester (1.02 g, 5.1194 mmol) in tetrahydrofuran (30 mL). Stir vigorously for 2 days at room temperature. Concentrate and treat with water (50 mL) and extract with diethyl ether (50 mL). Acidify the aqueous layer with 1 N hydrochloric acid (26 mL) and extract with diethyl ether (3 x 125 mL). Combine the organic extracts, dry (magnesium sulfate) and concentrate to give the title compound as a racemic mixture (0.84 g, 89%).

The compounds of Preparations 209-212 may be prepared essentially as described in Preparation 208 using fumaric acid and mesaconic acid.

| Prep | Compound |
|------|---|
| 209 | (E)-3-Dipropylcarbamoyl-2-methylacrylic acid |
| 210 | (E)-3-Dipropylcarbamoylacrylic acid |
| 211 | (E)-2-Methyl-3-(methylpropylcarbamoyl)-acrylic acid |
| 212 | (E)-3-Dimethylcarbamoyl-2-methylacrylic acid |

5

Preparation 213

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-phenoxyethyl-morpholine-4-carboxylic acid tert-butyl ester

(R)-2-phenoxyethyl-oxirane

Add phenol (1.089 g, 11.572 mmol) to a slurry of sodium hydride (0.347 g, 14.465 mmol) in N,N-dimethylformamide (77.1 mL) and stir at room temperature for 40 minutes. Add 3-nitrobenzenesulfonic acid (R)-1-oxiranemethyl ester (3.00 g, 11.572 mmol) and stir at room temperature for 16 hours (J. Org. Chem., 54, 1296-1304 (1989). Quench with saturated aqueous ammonium chloride (75 mL), dilute with water (75 mL) and extract with diethyl ether (3 x 300 mL). Combine the organic extracts, wash with saturated aqueous sodium bicarbonate (200 mL), saturated aqueous ammonium chloride (200 mL), dry (magnesium sulfate), filter and purify (silica gel chromatography, eluting with 10:90 to 50:50 ethyl acetate:hexanes) to give the desired compound as a clear liquid (1.410 g, 81.1%).

GC-MS = 150 [M]

20

(2R,3R,4S)-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-2-((R)-2-hydroxy-3-phenoxypropylamino)-pentan-1-ol

Add (R)-2-phenoxyethyl-oxirane (0.189 g, 1.258 mmol) to a solution of (2R,3R,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (0.205 g, 0.434 mmol) in ethanol (2.1 mL). Heat in a sealed vessel at 80 °C overnight. Concentrate and purify (silica gel chromatography, eluting with 1-1.5% 2 M ammonia in methanol/dichloromethane) to give the desired compound as a clear semi-solid (0.165 g, 56.9%).

25

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MS (ES): m/z = 668.0 [M+H]

(1R,2S,3S)-[2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethylbutyl]-(R)-(2-hydroxy-3-phenoxypropyl)-carbamic acid tert-butyl ester

- 5 Add di-tert-butyl dicarbonate (0.059 g, 0.271 mmol) and diisopropylethylamine (0.171 mL, 0.984 mmol) to a solution of (2R,3R,4S)-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-2-((R)-2-hydroxy-3-phenoxypropylamino)-pentan-1-ol (0.127 g, 0.246 mmol) in tetrahydrofuran (1.23 mL). Stir at room temperature overnight, add more di-tert-butyl dicarbonate (0.118 g) and stir for 2.5 days. Quench with water (20 mL),
10 extract with ethyl acetate (100 mL), wash with water (30 mL), saturated aqueous sodium chloride (30 mL), dry (magnesium sulfate), filter and purify (silica gel chromatography, eluting with 15:85 to 30:70 ethyl acetate:hexanes) to give the desired compound as a white foam (0.074 g, 39%).

MS (ES): m/z = 768.0 [M+H]

15

(R)-5-[(1R,2S,3S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-phenoxyethylmorpholine-4-carboxylic acid tert-butyl ester

- Dissolve (1R,2S,3S)-[2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethylbutyl]-(R)-(2-hydroxy-3-phenoxypropyl)-carbamic acid tert-butyl ester
20 (0.074 g, 0.096 mmol) in dry benzene (0.96 mL). Add tributylphosphine (0.029 g, 0.144 mmol), N,N-tetramethyl azodicarboxamide (0.025 g, 0.144 mmol) and more benzene (2 mL) to facilitate stirring. Stir at room temperature for 2 hours, concentrate and purify (silica gel chromatography, eluting with 10:90 to 15:85 ethyl acetate:hexanes) to give the desired compound as a white foam (0.032 g, 44.7%).

- 25 MS (ES): m/z = 750.0 [M+H]

(2R, 5R)-(5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-phenoxyethyl-morpholine-4-carboxylic acid tert-butyl ester

- Add 20% palladium hydroxide on carbon (0.032 g) to a solution of (R)-5-
30 [(1R,2S,3S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-phenoxyethylmorpholine-4-carboxylic acid tert-butyl ester (0.032 g, 0.043 mmol) in ethanol (0.43 mL). Stir vigorously under one atmosphere of hydrogen gas for 40 hours.

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Filter through a filtering agent, wash with ethanol and concentrate to give the desired compound.

(2R,5R)-5-[1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-phenoxymethylmorpholine-4-carboxylic acid tert-butyl ester

- 5 Add triethylamine (0.009 mL, 0.066 mmol) and acetic anhydride (0.004 mL, 0.044 mmol) to a solution of (2R, 5R)-5-[1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-phenoxymethyl-morpholine-4-carboxylic acid tert-butyl ester (0.021 g, 0.044 mmol) in tetrahydrofuran (0.44 mL) and stir at room temperature for 1 hour.
- 10 Concentrate and purify (silica gel chromatography, eluting with 50:50 to 60:40 ethyl acetate:hexanes) to give the title compound as a white foam (0.010 g, 45.5%).
- MS (ES): $m/z = 519.0$ [M-H]

Preparation 214

- 15 (R)-5-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester
- (2R,3R,4S)-3-benzyloxy-2-(3-benzyloxy-2-hydroxypropylamino)-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-(R)-ol
- Dissolve (2R,3R,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (7.440 g, 14.401 mmol) in ethanol (72 mL). Add (R)-2-benzyloxymethyl-oxirane (4.257 g, 25.921 mmol), flush with nitrogen and heat in a sealed vessel at 80 °C for 16 hours. Concentrate and purify (silica gel chromatography, eluting with 1.3% to 1.7% 2 M ammonia in methanol/dichloromethane) to give the desired compound as a clear semi-solid (7.520 g, 76.7%).
- 20 MS (ES): $m/z = 681.5$ [M+H]

(2S,3S)-[2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-(R)-1-hydroxymethylbutyl]-((R)-3-benzyloxy-2-hydroxypropyl)-carbamic acid tert-butyl ester

- Add di-tert-butyl dicarbonate (2.649 g, 12.150 mmol) and diisopropylethylamine (3.84 mL, 22.090 mmol) to a solution of (2R,3R,4S)-3-benzyloxy-2-(3-benzyloxy-2-hydroxypropylamino)-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-(R)-ol (7.52 g, 11.04 mmol) in tetrahydrofuran (55 mL) and heat at 50 °C for 2 days and stir at room
- 30

temperature for 2.5 days. Quench with water (175 mL), extract with ethyl acetate (800 mL), dry (magnesium sulfate), filter and purify (silica gel chromatography, eluting with 20:80 to 40:60 ethyl acetate:hexanes) to give the desired compound as a white foam (5.32 g, 61.7%).

5 MS (ES): m/z = 781.7 [M+H]

(1S,2S)-5-(R)-[1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(R)-benzyloxymethylmorpholine-4-carboxylic acid tert-butyl ester

Add N,N-tetramethyl azodicarboxamide (TMAD) (1.753 g, 10.180 mmol) and
10 tributylphosphine (2.540 mL, 10.180 mmol) to a solution of (2S,3S)-[2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-(R)-1-hydroxymethylbutyl]-((R)-3-benzyloxy-2-hydroxypropyl)-carbamic acid tert-butyl ester (5.300 g, 6.787 mmol) in benzene (34 mL) and stir vigorously for 1.5 hours. Filter the slurry, wash with hexanes, concentrate and purify (silica gel chromatography, eluting with 05:95 to 20:80 ethyl acetate:hexanes) to
15 give the desired compound as white foam (4.750 g, 91.7%).

MS (ES): m/z = 763.5 [M+H]

(R)-5-[2-(S)-Amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

20 Dissolve (1S,2S)-5-(R)-[1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(R)-benzyloxymethylmorpholine-4-carboxylic acid tert-butyl ester (4.750 g, 6.226 mmol) in ethanol (63 mL) and add 20% palladium hydroxide on carbon (4.750 g). Stir under one atmosphere of hydrogen gas for 42 hours, flush with nitrogen, dilute slurry with ethanol (175 mL), filter through a filtering agent, wash with ethanol and concentrate
25 to give the desired compound (2.213 g, 88.3%).

MS (ES): m/z = 403.3 [M+H]

(R)-5-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

30 Add triethylamine (0.623 mL, 4.473 mmol) and acetic anhydride (0.281 mL, 2.982 mmol) to a solution of (R)-5-[2-(S)-amino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (1.20

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g, 2.982 mmol) in tetrahydrofuran (30 mL). Stir at room temperature for 45 minutes, concentrate and purify (silica gel chromatography, eluting with 6:94 to 9:91 methanol:dichloromethane) to give the title compound as a white foam (0.906 g, 68.4%). MS (ES): $m/z = 445.3$ [M+H]

5

Preparation 215

(R)-5-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-2-fluorophenoxymethyl-morpholine-4-carboxylic acid tert-butyl ester

Dissolve (R)-5-[2-(S)-acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-
 10 2-(R)-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (0.040 g, 0.090 mmol) in acetonitrile (1.0 mL). Add diisopropyl azodicarboxylate (DIAD) (0.100 g, 0.495 mmol), then triphenylphosphine (0.130 g, 0.495 mmol) and 2-fluorophenol (0.050 g, 0.450 mmol). Stir at room temperature for 2 days and heat to 50 °C for 2 days, concentrate and purify twice (silica gel chromatography, eluting with 25:75 to 75:25 ethyl
 15 acetate:dichloromethane, then 1% to 3% methanol/dichloromethane) to give the title compound (0.005 g, 10.3%). MS (ES): $m/z = 537.3$ [M-H]

The compound of Preparations 216-217 may be prepared essentially as described
 20 in Preparation 215 using 3'-hydroxyacetophenone or 4'-hydroxyacetophenone.

| Prep. | Compound | MS (ES) [M+H] |
|-------|--|------------------|
| 216 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-acetylphenoxymethyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 563.3 |
| 217 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4-acetylphenoxymethyl)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 563.4 |

Preparation 218

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymethylmorpholine-4-carboxylic acid tert-butyl ester

25 (R)-2-Cyclohexyloxymethyl-oxirane

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In two separate runs, dissolve (R)-2-phenoxyethyl-oxirane (1.410 g, 9.389 mmol) in tetrahydrofuran (50 mL). Add 5% ruthenium on carbon (0.71 g) and hydrogenate at 60 psi of hydrogen gas for 40 minutes. Filter through a filtering agent, wash with tetrahydrofuran, concentrate and purify (silica gel chromatography, eluting with 5:95 to 30:70 ethyl acetate:hexanes) to give the desired compound as a clear liquid (0.850 g, 57.9% combined yield).

(2R,3R,4S)-3-benzyloxy-2-((R)-3-cyclohexyloxy-2-hydroxypropylamino)-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol

10 Add (R)-2-cyclohexyloxymethyl-oxirane (0.688 g, 4.402 mmol) to a solution of 2-amino-3-(R)-benzyloxy-4-(S)-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-(R)-ol (1.300 g, 2.751 mmol) in ethanol (13.76 mL). Flush with nitrogen and heat in a sealed tube at 80 °C overnight. Concentrate and purify (silica gel chromatography, eluting with 1.3% to 1.8% 2 M ammonia in methanol/dichloromethane) to give the desired compound
15 as a yellow semi-solid (1.140 g, 61.6%).
MS (ES): $m/z = 673.6$ [M+H]

[(1R,2S,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethyl-butyl]-((R)-3-cyclohexyloxy-2-hydroxypropyl)-carbamic acid tert-butyl ester

20 Dissolve (2R,3R,4S)-3-benzyloxy-2-((R)-3-cyclohexyloxy-2-hydroxypropylamino)-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (1.140 g, 1.694 mmol) in tetrahydrofuran (8.5 mL) followed by the addition of di-tert-butyl dicarbonate (0.406 g, 1.864 mmol) and diisopropylethylamine (0.589 mL, 3.389 mmol). Heat to 50 °C for 2.5 days, quench with water (60 mL), extract with ethyl acetate, dry
25 (magnesium sulfate) and purify (silica gel chromatography, eluting with 20:80 to 40:60 ethylacetate:hexanes) to give the desired compound (0.948 g, 72.4%).
MS (ES): $m/z = 773.6$ [M+H]

(2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-cyclohexyloxymethyl-morpholine-4-carboxylic acid tert-butyl ester

30 Dissolve [(1R,2S,3S)-2-benzyloxy-3-dibenzylamino-4-(3,5-difluorophenyl)-1-hydroxymethyl-butyl]-((R)-3-cyclohexyloxy-2-hydroxypropyl)-carbamic acid tert-butyl

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ester (0.940 g, 1.216 mmol) in benzene (6 mL) followed by the addition of tributylphosphine (0.369 g, 1.824 mmol) and N,N-tetramethyl azodicarboxamide (TMAD) (0.314 g, 1.824 mmol). Stir vigorously for 16 hours, filter the slurry, wash with hexanes and purify (silica gel chromatography, eluting with 5:95 to 15:85 ethyl acetate:hexanes) to give the desired compound as a white foam (0.777 g, 84.7%).
MS (ES): $m/z = 755.6$ [M+H]

(2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymethylmorpholine-4-carboxylic acid tert-butyl ester

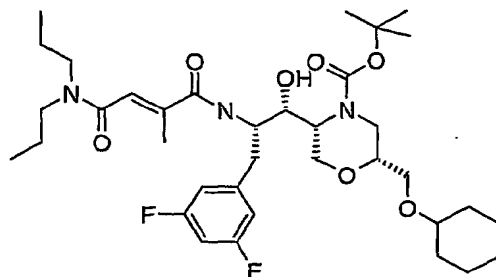
10 Add 20% palladium hydroxide on carbon (0.772 g) to a solution of (2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-cyclohexyloxymethyl-morpholine-4-carboxylic acid tert-butyl ester (0.772 g, 1.023 mmol) in ethanol (10.2 mL). Stir vigorously under 1 atmosphere of hydrogen gas for 60 hours. Filter through a filtering agent, wash with ethanol and concentrate to give the
15 desired compound (0.481 g, 97.1%).
MS (ES): $m/z = 485.4$ [M+H]

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymethylmorpholine-4-carboxylic acid tert-butyl ester

20 Dissolve (2R,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymethylmorpholine-4-carboxylic acid tert-butyl ester (0.240 g, 0.495 mmol) in tetrahydrofuran (5 mL) and cool to 0 °C. Add triethylamine (0.104 mL, 0.743 mmol) and acetic anhydride (0.047 mL, 0.495 mmol) and stir for 90 minutes. Concentrate and purify (silica gel chromatography, eluting with 2:98 to 3:97
25 methanol:dichloromethane) to give the title compound as a white foam (0.209 g, 80.1%).
MS (ES): $m/z = 527.4$ [M+H]

Preparation 219

-99-



(2R,5R)-2-Cyclohexyloxymethyl-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-((E)-3-dipropylcarbamoyl-2-methylacryloylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid tert-butyl ester

- 5 Dissolve (E)-3-dipropylcarbamoyl-2-methylacrylic acid (0.029 g, 0.134 mmol) in dichloromethane (1.3 mL). Add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.028 g, 0.148 mmol) then 1-hydroxybenzotriazole (HOBT) (0.023 g, 0.148 mmol). Stir at room temperature for 30 minutes. To this stirring solution add (2R,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexyloxymethylmorpholine-4-carboxylic acid tert-butyl ester (0.065 g, 0.134 mmol) in
- 10 dichloromethane (1.5 mL). Stir for 2.5 hours, quench with 10% aqueous potassium carbonate (20 mL), and dilute with dichloromethane (75 mL). Extract the organic layer, wash with 5% aqueous citric acid (25 mL), saturated aqueous sodium chloride (30 mL), dry (magnesium sulfate) and purify (silica gel chromatography, eluting with 30:70 to
- 15 70:30 ethyl acetate:hexanes) to give the title compound as a white foam (0.041 g, 45.2%). MS (ES): m/z = 680.6 [M+H]

The compounds of Preparations 220-286 may be prepared essentially as described in Preparation 219.

| Prep | Compound | MS (ES) [M+H] |
|------|--|------------------|
| 220 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-[(E)-3-(dipropylcarbamoyl)-acryloylamino]-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 665.5 |
| 221 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(3,3,3-trifluoropropionylamino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 593.3 |
| 222 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-((E)-3-dimethylcarbamoyl-2-methylacryloylamino)-1- | 624.4 |

| | | |
|-----|---|-----------------|
| | hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 223 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-[(E)-2-methyl-3-(methylpropylcarbamoyl)-acryloylamino]-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 652.5 |
| 224 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-((E)-5,5-dimethyl-4-oxohex-2-enoylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 621.3 [M-H] |
| 225 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-((E)-4,4,4-trifluorobut-2-enoylamino)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 579.2 [M-H] |
| 226 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-[(<u>trans</u> -2-(methylpropylcarbamoyl)-cyclopropanecarbonyl]-amino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomers 1 and 2 | 652.5 652.5 |
| 227 | (2R,3S,5R)-5-[2-(4,4-difluoro-6-methylheptanoylamino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 635.5 |
| 228 | (2R,5R)-5-[2-(4,4-difluoro-6-methylheptanoylamino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 621.5 |
| 229 | (2R,5R)-5-[2-(<u>trans</u> -(2-fluoromethylcyclopropanecarbonyl)amino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomers 1 and 2 | 557.3 557.3 |
| 230 | (2R,5R)-5-[2-(5,5,5-trifluoropentanoylamino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 595.4 [M-H] |
| 231 | (2R,5R)-5-[2-(4,5,5-trifluoropent-4-enoylamino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 593.5 [M-H] |
| 232 | (2R,5R)-5-[2-(<u>trans</u> -(2,2-difluoromethylcyclopropanecarbonyl)-amino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomers 1 and 2 | 575.0 [M-H] |
| 233 | (2R,5R)-5-{2-[<u>cis</u> -2-(methyl-propyl-carbamoyl)cyclopropanecarbonyl]amino-3-(3,5-difluorophenyl)-1-hydroxy-propyl}-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomers 1 and 2 | 624.3 [M-H] |
| 234 | (2R,5R)-5-[2-((2,2-difluoropropionyl)amino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 549.3 [M-H] |
| 235 | (2R,5R)-5-[2-((2-fluoropropionyl)amino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester-Isomers 1 and 2 | 531.2 [M-H] |
| 236 | (2R,5R)-5-[2-((4,4,4-trifluorobutyryl)amino)-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.3 [M+Na] |
| 237 | (2R,5R)-5-[2-(((E)-4,4,4-trifluoro-2-methyl-but-2-enoyl)amino)-3- | 593.3 |

| | | |
|-----|--|--------|
| | (3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | [M-H] |
| 238 | (2R,5R)-5-[(1S,2S)-2-Benzoylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 589.38 |
| 239 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluoro-phenyl)-2-(2,2-dimethylpropionylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 569.41 |
| 240 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluoro-phenyl)-1-hydroxy-2-isobutyrylamino-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 555.39 |
| 241 | (2R,5R)-5-[(1S,2S)-2-(Cyclobutanecarbonylamino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxy-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.51 |
| 242 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-2-(cyclopropane-carbonylamino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553.46 |
| 243 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-[(thiophene-2-carbonyl)-amino]-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 595.47 |
| 244 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(2-methoxyacetyl-amino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 557.3 |
| 245 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-2-(2-cyclopropylacetyl-amino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567.56 |
| 246 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-(3,3-dimethylbutyrylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 583.39 |
| 247 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(3-methoxypropionylamino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 571.4 |
| 248 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-(3-fluorobenzoylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 607.5 |
| 249 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(3-propoxybenzoylamino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 647.6 |
| 250 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluoro-phenyl)-1-hydroxy-2-[(R)-tetrahydrofuran-2-carbonyl]-amino]-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 583.5 |
| 251 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-(2-fluorobenzoylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 607.5 |
| 252 | (2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(3-methylbenzoylamino)-propyl]-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 603.5 |

| | | |
|-----|---|--------------------------|
| 253 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-octanoylamino-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 585.4 |
| 254 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-(5-methyl-hexanoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 571.56 |
| 255 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-[(2,5-dimethyl-furan-3-carbonyl)-amino]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 581.45 |
| 256 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-heptanoylamino-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 571.52 |
| 257 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-2-methyl-5-propyl-octa-2,4-dienoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 637.69 |
| 258 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-[(E)-3-methyl-3-(methyl-propyl-carbamoyl)-but-2-enoylamino]-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 626.59 |
| 259 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-[3-(methyl-propyl-carbamoyl)-propionylamino]-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 614.7 |
| 260 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-2-methyl-hex-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 469.7 [M+1- BOC] |
| 261 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-(5,5-dimethyl-4-oxo-hexanoylamino)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 599.49 |
| 262 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-[3-(ethyl-propyl-carbamoyl)-propionylamino]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 628.75 |
| 263 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(1-methyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 527.37 |
| 264 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-[[5-(methyl-propyl-carbamoyl)-furan-2-carbonyl]-amino]-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 652.52 |
| 265 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-(4-methyl-pentanoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 557.43 |
| 266 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-(6-methyl-4-oxo-heptanoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 599.41 |
| 267 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-pentyloxycarbonylamino-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 517.23 [M+1-t- Bu] |
| 268 | (2R,5R)-5-[(1S,2S)-2-Butoxycarbonylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4- | 503.30 [M+1-t- |

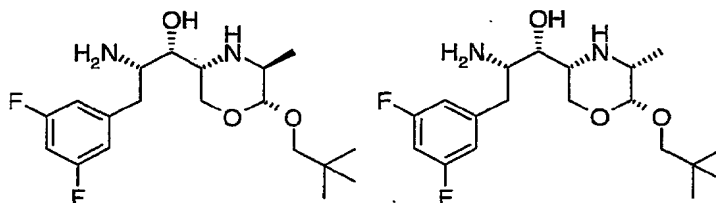
| | | |
|-----|--|-------------------------|
| | carboxylic acid tert-butyl ester | Bu] |
| 269 | (2R,5R)-5-[(1S,2S)-2-[(5-tert-Butyl-2-methyl-furan-3-carbonyl)-amino]-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 623.46 |
| 270 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-(4-oxo-hexanoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 571.48 |
| 271 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-3,5,5-trimethyl-4-oxo-hex-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 644.42 |
| 272 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-2-methyl-oct-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 597.5 |
| 273 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-(3-dipropylcarbamoyl-propionylamino)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 642.54 |
| 274 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-hexyloxycarbonylamino-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 487.35 [M+1- BOC] |
| 275 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-2-methyl-4-oxo-hept-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 597.52 |
| 276 | (2R,5R)-5-[(1S,2S)-2-(4-Cyclopentyl-4-oxo-butyrylamino)-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | |
| 277 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-(5,5-dimethyl-hexanoylamino)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 585.44 |
| 278 | (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-2,4,4-trimethyl-hept-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 611.49 |

The compounds of Preparations 279 – 286 may be prepared essentially as described in Preparation 98.

| Prep | Compound | MS (ES) [M+H] |
|------|--|------------------|
| 279 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(4-methyl-tetrahydro-pyran-4-ylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 543.7 |
| 280 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(bicyclo[2.2.1]hept-1-ylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 539.4 |
| 281 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(1-methyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 527.37 |

| | | |
|-----|---|--------|
| 282 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester | 609.41 |
| 283 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-butoxy)-morpholine-4-carboxylic acid tert-butyl ester | 515.48 |
| 284 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-pentyloxy)-morpholine-4-carboxylic acid tert-butyl ester | |
| 285 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(1-phenyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester | |
| 286 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2,4-trimethyl-pentyloxy)-morpholine-4-carboxylic acid tert-butyl ester | 543.32 |

Preparation 287



(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5R,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol

(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol

1-bis-(2,2-dimethylpropoxy)-propan-2-one

Combine pyruvicaldehyde dimethyl acetal (7 mL, 59 mmol), neopentyl alcohol (12.7 g, 144 mmol), and *p*-toluenesulfonic acid monohydrate (0.6 g, 3.2 mmol) and heat for 21 hours at 80 °C. Cool to room temperature and purify (silica gel chromatography using deactivated silica gel, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give a yellow liquid (8.0 g).

¹H NMR (400 MHz, CDCl₃) δ 4.34 (s, 1H), 3.32 (d, J = 8.0 Hz, 2H), 3.10 (d, J = 8.8 Hz, 2H), 2.19 (s, 3H), 0.93 (s, 18 H).

(2R,3R,4S)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol

(2R,3R,4S)-3-benzyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol

Suspend (2R,3R,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (2.7 g, 5.2 mmol), 1-bis-(2,2-dimethylpropoxy)-propan-2-one (3.0 g, 13 mmol), pyridinium p-toluene sulphonate (148 mg, 0.59 mmol), and freshly
 5 one (3.0 g, 13 mmol), pyridinium p-toluene sulphonate (148 mg, 0.59 mmol), and freshly activated 3 Å molecular sieves (800 mg) in dry toluene (20 mL) under nitrogen and heat to reflux for 17 hours. Filter, concentrate, dissolve the residue in dry methanol (30 mL) and cool to 0 °C. Add sodium cyanoborohydride (1.28 g, 20 mmol) followed by the dropwise addition of glacial acetic acid (0.63 mL, 11 mmol). Stir for 15 minutes, then
 10 remove the cooling bath and allow to warm to room temperature. After 45 minutes dilute with ethyl acetate and add 2 N sodium hydroxide (25 mL). Stir the mixture for 15 minutes, separate away the aqueous phase, wash the organic solution with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, dry (sodium sulfate), filter and concentrate. Deactivate the silica gel by thorough washes with 3% 2 M
 15 ammonia in methanol/dichloromethane, dichloromethane and then with hexanes. Purify (deactivated silica-gel chromatography using deactivated silica gel, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the desired compounds in order of elution:
 (2R,3R,4S)-3-benzyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (1.19 g, 30 %, MS (ES) 731.5 *m/z* [M+H]); followed by (2R,3R,4S)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (1.13 g, 30%,
 20 MS (ES): *m/z* = 731.5 [M+H]).

Dibenzyl-[(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl]-amine
 25 Dibenzyl-[(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6S)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl]-amine

Add distilled boron trifluoride diethyl etherate (2.8 mL, 22 mmol) dropwise to a solution of (2R,3R,4S)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (5.8 g, 7.9
 30 mmol) in dry 1,2-dichloroethane (350 mL) under nitrogen and reflux for 1 hour. Cool to room temperature and dilute with ethyl acetate and saturated aqueous sodium bicarbonate

solution. Shake the mixture vigorously, separate away the aqueous, wash the organic solution with saturated aqueous sodium bicarbonate solution (twice) and set aside.

Combine the aqueous solutions and extract with ethyl acetate (twice). Combine the organic extracts, wash with saturated aqueous sodium chloride solution, dry (sodium

- 5 sulfate), filter, concentrate and purify (silica gel chromatography using deactivated silica-gel, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give in order of elution: dibenzyl-{(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6S)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl}-amine (0.36 g, 7%, MS (ES): m/z = 643 [M+H]); followed by dibenzyl-{(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-
10 [(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl}-amine (3.78 g, 74%, MS (ES): m/z = 643.5 [M+H])

Dibenzyl-{(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5R,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl}-amine

- 15 Prepare the desired compound essentially as described above starting from (2R,3R,4S)-3-benzyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol (57%).
MS (ES): m/z = 643.5 [M+H]

- 20 (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol

- Add 20% palladium hydroxide on carbon (679 mg) to a solution of dibenzyl-{(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl}-amine (284 mg, 0.442 mmol) in absolute ethanol (5 mL)
25 and stir under 1 atmosphere of hydrogen gas at room temperature for 18 hours. Filter through a pad of Celite®, wash thoroughly with ethanol and concentrate to give the desired compound as a glass (162 mg, 98%).
MS (ES): m/z = 373.3 [M+H]

- 30 (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5R,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol

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Prepare the title compound essentially as described above starting from dibenzyl-
 {(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5R,6R)-6-(2,2-dimethylpropoxy)-5-
 methylmorpholin-3-yl]-ethyl}-amine (93%).

MS (ES): $m/z = 373.3$ [M+H]

5

The compounds of Preparation 288-294 may be prepared essentially as described
 in Preparation 287. The compound of Preparation 288 may be prepared using
 camphorsulfonic acid instead of boron trifluoride diethyl etherate. The acetals necessary
 for the preparation of compounds of Preparations 289-294 may be prepared essentially as
 described in *J. Am. Chem. Soc.*, 78(16), 4161 (1956).

10

| Prep | Compound |
|------|---|
| 288 | (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-isobutyl-morpholin-3-yl]-propan-1-ol |
| 289 | (1S,2S)-2-Amino-1-[(3R,6R)-5-cyclopropylmethyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-3-(3,5-difluorophenyl)-propan-1-ol |
| 290 | (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-5-methyl-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-propan-1-ol |
| 291 | (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-5-methyl-6-(1-methylcyclopropylmethoxy)-morpholin-3-yl]-propan-1-ol |
| 292 | (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2-ethyl-2-methylbutoxy)-5-methylmorpholin-3-yl]-propan-1-ol |
| 293 | (1S,2S)-2-Amino-1-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-3-phenylpropan-1-ol |
| 294 | (1S,2S)-2-Amino-3-(3,5-difluoro-phenyl)-1-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-propyl-morpholin-3-yl]-propan-1-ol |

Preparation 295

(1-Fluorocyclohexyl)-methanol

Prepare the title compound essentially as described in the literature procedure

15 Synthesis, 1988, 310-313.

Preparation 296

(4-Fluorotetrahydropyran-4-yl)-methanol

1,6-Dioxa-spiro[2.5]octane-2-carbonitrile

20 Dissolve tetrahydropyran-4-one (5.0 mL, 54.2 mmol) and chloroacetonitrile (3.4 mL, 53.5 mmol) in tert-butanol (1 mL) and add drop-wise a solution of potassium tert-

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butoxide (54 mL, 54 mmol, 1.0 M in tert-butanol) over 20 minutes. Stir for 16 hours, dilute with water and quench slowly with 1 N hydrochloric acid. Extract with diethyl ether (x3). Combine extracts and wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting
5 with 0:100 to 1:1 ethyl acetate:hexanes) to give the desired compound as a light yellow oil (4.4g, 59%).

¹H NMR (400 MHz, CDCl₃) δ 3.89-3.87 m (2H), 3.85-3.82 (m, 2H), 3.33 (s, 1H), 2.13-2.06 (m, 1H), 1.93-1.79 (m, 2H), 1.62-1.54 (m, 1H).

10 (4-Fluorotetrahydropyran-4-yl)-hydroxyacetonitrile

Dissolve 1,6-dioxaspiro[2.5]octane-2-carbonitrile (4.14 g, 29.8 mmol) in dry dichloromethane (10 mL) and cool to 0 °C under a nitrogen atmosphere in a polypropylene bottle. Add hydrogen fluoride-pyridine (3 mL) dropwise. Allow the mixture to slowly warm to room temperature over 3 h and then stir an additional 1.5
15 hours at room temperature. Pour into ethyl acetate and wash with saturated aqueous sodium bicarbonate solution until washes remain basic. Combine the aqueous washes and adjust the pH of the solution to ~pH = 8 and extract with ethyl acetate. Combine this organic extract with the ethyl acetate solution of the crude reaction mixture and wash with saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter and
20 concentrate to give the desired compound as a yellow oil which is used directly in the next reaction.

(4-Fluorotetrahydropyran-4-yl)-methanol

Dissolve (4-fluorotetrahydropyran-4-yl)-hydroxyacetonitrile (4.4 g, 29.8 mmol) in
25 2-propanol (48 mL) and water (12 mL). Cool to 0 °C under a nitrogen atmosphere. Add sodium borohydride (1.2 g, 31.7 mmol) and allow the resulting mixture to slowly warm to room temperature over 5.5 hours. Quench with acetone and stir for 1 h. Concentrate the mixture to 1/3 volume and dilute with ethyl acetate. Wash the resulting organic solution with saturated aqueous sodium bicarbonate solution and saturated aqueous ammonium
30 chloride solution (twice). Combine the aqueous washes and dilute with saturated aqueous sodium chloride solution and extract with ethyl acetate (twice). Add these extracts to the

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crude reaction mixture and wash the resulting solution with saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 1:1 ethyl acetate:hexanes) to give the desired compound as a yellow oil (740 mg, 18%).

- 5 ^1H NMR (400 MHz, CDCl_3) δ 3.83 (ddd, $J = 2.8, 5.6, 11.6$ Hz, 2H), 3.72 (ddd, $J = 2.8, 11.2, 11.2$ Hz, 2H), 3.68 (s, 1H), 3.58 (s, 1H), 1.88-1.63 (m, 5H)

Preparation 297

Cis-3-*tert*-butylcyclobutanol10 3-*tert*-butyl-2,2-dichlorocyclobutanone

- Suspend 3,3-dimethyl-1-butene (10 mL, 80.8 mmol), ethylene glycol dimethyl ether (11.5 mL, 106 mmol), and freshly activated zinc (13.8 g, 211 mmol) in dry diethyl ether (100 mL) under a nitrogen atmosphere. Add to this suspension a solution of trichloroacetyl chloride (11.5 mL, 103 mmol) in dry diethyl ether (50 mL) dropwise over
15 20 minutes. Heat to reflux for 24 hours. Cool to room temperature and filter off the residual solid materials. Concentrate the filtrate and triturate the residue with hexanes. Filter the mixture to remove solid materials. Wash the filtrate solution with saturated aqueous sodium bicarbonate solution (3x), saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting
20 with 0:100 to 10:90 ethyl acetate:hexanes) to give the pure fractions and concentrate. Isolate the desired compound by vacuum distillation to give a clear liquid (7.59 g, 48%).
 ^1H NMR (400 MHz, CDCl_3) δ 3.29 (app. dd, $J = 7.2, 10.4$ Hz, 2H), 2.83 (dd, $J = 10.0, 11.2$ Hz, 1H), 1.14 (s, 9H)

25 3-*tert*-butylcyclobutanone

- Saturate dry methanol by stirring with excess ammonium chloride under nitrogen for 1.5 h. Add this saturated solution (150 mL) to 3-*tert*-butyl-2,2-dichlorocyclobutanone (7.5 g, 38.4 mmol) under nitrogen. To the resulting suspension add freshly activated zinc (15.4 g, 236 mmol). Stir for 5 hours, filter and concentrate. Partition the residue between
30 diethyl ether and water. Discard the aqueous phase and wash the diethyl ether layer with water (twice), saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter,

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concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the desired compound as a clear liquid (2.71 g, 56%).

^1H NMR (400 MHz, CDCl_3) δ 2.87 (m, 4H), 2.30 (m, 1H), 0.93 (s, 9H)

5 Cis-3-tert-butylcyclobutanol

- Cool lithium aluminum hydride (16 mL, 16 mmol, 1.0 M solution in tetrahydrofuran) under a nitrogen atmosphere to 0 °C. Add tert-butanol (4.6 mL, 48.1 mmol) dropwise, warm to room temperature, and stir the resulting solution for 1 hour. Cool the hydride solution to -78 °C and add a solution of 3-tert-butylcyclobutanone (1 g, 7.9 mmol) in dry tetrahydrofuran (3 mL) dropwise. Stir for 1 hour at -78 °C and then warm to room temperature over 1 hour. Slowly quench the mixture with 0.1 N hydrochloric acid. Dilute the resulting mixture with ethyl acetate and a saturated aqueous solution of sodium potassium tartrate (Rochelle salt) and stir the biphasic mixture overnight. Filter the mixture to remove precipitates and separate the aqueous layer.
- 10 15 Saturate the aqueous phase with sodium chloride and extract with ethyl acetate. Add the organic extract to the ethyl acetate solution of the reaction mixture and wash the resultant mixture with saturated aqueous sodium chloride solution, dry (magnesium sulfate), filter, and concentrate to give the title compound as a ~9:1 mixture of cis/trans diastereomers.
- 20 ^1H NMR (400 MHz, CDCl_3) δ 3.99 (m, 1H), 2.17-2.15 (m, 2H), 1.56-1.51 (m, 3H), 0.78 (s, 9H).

Preparation 298

(R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

- 25 [(R)-2-(tert-butyl-dimethylsilyloxy)-1-(1-ethoxy-2-iodoethoxymethyl)-ethyl]-carbamic acid tert-butyl ester

- Dissolve [(R)-1-(tert-butyl-dimethylsilyloxymethyl)-2-hydroxyethyl]-carbamic acid tert-butyl ester (1.0 g, 3.27 mmol) and ethyl vinyl ether (0.20 g, 2.73 mmol) in acetonitrile (20 mL) and add N-iodosuccinimide (0.735 g, 3.27 mmol). Stir at room temperature 72 hours and pour into saturated aqueous sodium chloride. Extract with ethyl acetate, wash with water and saturated aqueous sodium chloride, dry (magnesium
- 30

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sulfate), filter and concentrate. Purify on silica gel, eluting with 0:100 to 10:90 ethyl acetate:hexanes to give the desired compound.

MS (ES): m/z = 504.4 [M+H]

5 (R)-5-(tert-butyldimethylsilyloxyethyl)-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

Add sodium hydride (0.044 g, 1.10 mmol) to [(R)-2-(tert-butyldimethylsilyloxy)-1-(1-ethoxy-2-iodoethoxymethyl)-ethyl]-carbamic acid tert-butyl ester (0.462 g, 0.918 mmol) in N,N-dimethylformamide (9 mL) at room temperature. Heat to ~50 °C for 10 4 hours, cool to room temperature, and pour into ethyl acetate. Wash with water, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Purify on silica gel, eluting with 0:100 to 50:50 ethyl acetate:hexanes to give the desired compound as a mixture of diastereomers.

¹HNMR (400 MHz, CDCl₃) (more polar diastereomer) δ 4.69 (bs, 1H), 3.98-3.45 (m, 8H), 3.07 (d, J = 12.8 Hz, 1H), 1.46 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

(S)-2-Ethoxy-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve (R)-5-(tert-butyldimethylsilyloxyethyl)-2-ethoxymorpholine-4- 20 carboxylic acid tert-butyl ester (0.39 g, 1.04 mmol) in tetrahydrofuran (3 mL) and add tetrabutylammonium fluoride (2.1 mL, 2.1 mmol, 1.0 M in tetrahydrofuran). Stir 45 minutes at room temperature and concentrate. Purify on silica gel, eluting with 10:90 to 40:60 ethyl acetate in hexanes to give the desired compound.

¹HNMR (400 MHz, CDCl₃) δ 4.69 (bs, 1H), 4.08-4.04 (m, 2H), 3.88-3.66 (m, 4H), 3.56 (d, J = 10.8 Hz, 1H), 3.51-3.43 (m, 1H), 3.20 (d, J = 14 Hz, 1H), 1.47 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H)

(R)-5-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

30 To (S)-2-ethoxy-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (0.245 g, 0.938 mmol) in dimethylsulfoxide (3 mL) at room temperature add triethylamine (0.180 g, 1.78 mmol), then pyridine sulfur trioxide complex (0.283 g, 1.78

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mmol) in dimethylsulfoxide (1.5 mL). Stir at room temperature 4 hours and pour into 50 mL of 10:90 ethyl acetate/hexanes. Wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate. Dissolve the residue in tetrahydrofuran (1.5 mL) and add 3,5-difluorophenyl nitroethane (0.134 g, 0.725 mmol).

- 5 Cool in an ice/water bath and add tetrabutylammonium fluoride (0.70 mL, 0.70 mmol, 1.0 M in tetrahydrofuran) all at once. Stir 30 minutes and pour into cold half saturated aqueous sodium chloride (~20 mL). Extract with ethyl acetate, wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), and concentrate. Purify on silica gel, eluting with 0:100 to 30:70 ethyl acetate:hexanes to give the desired compound.
- 10 MS (ES): $m/z = 445.2$ [M-H]

(R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

- To a solution of (R)-5-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.145 g, 0.325 mmol) in methanol (5 mL) at room temperature add nickel (II) chloride (0.063 g, 0.487 mmol) and then sodium borohydride (0.061 g, 1.62 mmol) portionwise. Stir 30 minutes, add water (~3 mL) and concentrate. Dilute with ethyl acetate and filter through Celite®. Partition the filtrate between ethyl acetate and water. Dry the ethyl acetate layer (magnesium sulfate),
- 15 2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.145 g, 0.325 mmol) in methanol (5 mL) at room temperature add nickel (II) chloride (0.063 g, 0.487 mmol) and then sodium borohydride (0.061 g, 1.62 mmol) portionwise. Stir 30 minutes, add water (~3 mL) and concentrate. Dilute with ethyl acetate and filter through Celite®. Partition the filtrate between ethyl acetate and water. Dry the ethyl acetate layer (magnesium sulfate),
- 20 filter and concentrate to give the desired compound as a white solid.
- MS (ES): $m/z = 417.3$ [M+H]

(R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

- 25 Add triethylamine (0.030 g, 0.30 mmol) and acetic anhydride (0.024 g, 0.23 mmol) to (R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.095 g, 0.228 mmol) in tetrahydrofuran (4 mL) at room temperature. Stir 4 hours and dilute with ethyl acetate. Wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate. Purify on silica gel, eluting with 20:80 to 100% ethyl acetate:hexanes to give the title compound.
- 30 MS (ES): $m/z = 457.2$ [M+H]

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Preparation 299

(R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester

5 [(S)-2-benzyloxy-1-(2-iodo-1,1-diphenylethoxymethyl)-ethyl]-carbamic acid tert-butyl ester

Dissolve ((R)-2-benzyloxy-1-hydroxymethylethyl)-carbamic acid tert-butyl ester (1.0 g, 3.55 mmol) and 1,1-diphenylethylene (0.534 g, 2.96 mmol) in acetonitrile (20 mL). Add N-iodosuccinimide (0.800 g, 3.55 mmol) and stir at room temperature 72
10 hours. Pour into ethyl acetate and wash with saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Purify on silica gel, eluting with 0:100 to 30:70 ethyl acetate:hexanes to give the desired compound.

¹HNMR (400 MHz, CDCl₃) δ 7.37-7.21 (m, 15 H), 5.04 (d, J = 7.6 Hz, 2H), 4.13 (s, 3H), 4.04 (bs, 1H), 3.76-3.66 (m, 2H), 3.32-3.23 (m, 2H), 1.43 (s, 9H)

15

(S)-5-benzyloxymethyl-2,2-diphenyl-morpholine-4-carboxylic acid tert-butyl ester

To [(S)-1-benzyloxymethyl-2-(2-iodo-1,1-diphenylethoxy)-ethyl]-carbamic acid tert-butyl ester (4.74 g, 8.07 mmol) in N,N-dimethylformamide (70 mL) at room temperature add sodium hydride (0.452 g, 11.3 mmol, 60% dispersion in mineral oil).
20 Heat reaction mixture to 60°C for 4 hours, cool to room temperature and dilute with ethyl acetate (~400 mL). Wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate. Purify on silica gel eluting with 0:100 to 20:80 ethyl acetate:hexanes to give the desired compound as an oil.

MS (ES): *m/z* = 460.4 [M+H]

25

(R)-5-Formyl-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester

To 10% palladium on carbon (2.1 g) in ethanol (50 mL) add (S)-5-benzyloxymethyl-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester (3.29 g, 7.16 mmol) in ethanol (75 mL) and stir under 1 atmosphere of hydrogen gas at room
30 temperature for 4 hours. Filter and concentrate to give the desired compound as a white solid. Dissolve the solid in dimethylsulfoxide (20 mL) and add triethylamine (1.30 g, 12.82 mmol), then pyridine sulfur trioxide complex (1.84 g, 11.55 mmol). Stir at room

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temperature 3 hours and dilute with 10% ethyl acetate/hexanes (~150 mL). Wash with water, 1 N aqueous citric acid and saturated aqueous sodium chloride, dry (magnesium sulfate), filter and concentrate to give the desired compound as a white solid.

MS (ES): m/z = 268.2 [M-BOC+H]

5

(R)-5-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester

To (R)-5-formyl-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester (1.03 g, 2.80 mmol) and 1,3-difluoro-5-(2-nitroethyl)-benzene (0.577 g, 3.08 mmol) in
10 tetrahydrofuran (5 mL) at ~0 °C under nitrogen add tetrabutylammonium fluoride (3 mL, 3.0 mmol, 1.0 M in tetrahydrofuran). Stir 20 minutes and add half saturated aqueous sodium chloride (~20 mL) and ethyl acetate (~100 mL). Separate the layers and wash the organic layer with water and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Purify on silica gel, eluting with 0:100 to 50:50 ethyl
15 acetate:hexanes, then re-crystallize from hexanes/dichloromethane to give the desired compound.

MS (ES): m/z = 455.3 [M-BOC+H]

20 (R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve (R)-5-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester (0.172 g, 0.31 mmol) in dry methanol (8 mL), add nickel chloride (0.060 g, 0.46 mmol) then sodium borohydride (0.059 g, 1.55 mmol). Stir 15 minutes, add water (~2 mL) and concentrate. Add ethyl
25 acetate (~70 mL), filter (Celite®), wash with water and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate to give the desired compound as a white solid.

MS (ES): m/z = 525.3 [M+H]

30 (R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester

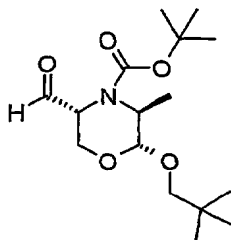
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Dissolve (R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-diphenylmorpholine-4-carboxylic acid tert-butyl ester (0.163 g, 0.31 mmol) in tetrahydrofuran (4 mL). Add triethylamine (0.044 g, 0.44 mmol) and acetic anhydride (0.036 g, 0.35 mmol). Stir 90 minutes and dilute with ethyl acetate (50 mL). Wash with 0.1 N aqueous citric acid, water, and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Purify on silica gel, eluting with 10:90 to 50:50 ethyl acetate:hexanes to give the title compound.

MS (ES): m/z = 467.3 [M-BOC+H].

10

Preparation 300



(2R,3S,5R)-2-(2,2-Dimethylpropoxy)-5-formyl-3-methylmorpholine-4-carboxylic acid
tert-butyl ester

1,1-bis-(2,2-dimethylpropoxy)-propan-2-one

15 Add p-toluenesulfonic acid hydrate (1.21 g, 10.58 mmol) to 1,1-dimethoxypropan-2-one (25.00 g, 211.63 mmol) and neopentyl alcohol (46.64 g, 529.08 mmol) at room temperature. Heat in an open flask in an 80 °C oil bath for 8 hours. Allow to cool to room temperature and stir over the weekend. Purify (silica gel chromatography, eluting with 0:100 to 8:92 ethyl acetate:hexanes) to give the desired compound as a colorless oil (32.78 g 67.2%)

20

(R)-3-benzyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol

(R)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol

25 Add pyridinium p-toluenesulfonate (PPTS) (0.57 g, 2.25 mmol) and 3Å molecular sieves (0.73 g) to (R)-2-amino-3-benzyloxypropan-1-ol (4.08 g, 22.51 mmol) and 1,1-bis-(2,2-dimethylpropoxy)-propan-2-one (8.30 g, 36.02 mmol) in dry toluene (90 mL) and reflux under nitrogen for 2 hours. Cool to room temperature, filter and concentrate.

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Dissolve in dry methanol (90 mL) and add sodium cyanoborohydride (5.66 g, 90.05 mmol) followed by acetic acid (2.5 mL) dropwise. Stir 30 minutes and concentrate. Dilute with ethyl acetate (~200 mL) and add water (~10 mL) followed by 1 N sodium hydroxide (~50 mL). Stir 20 minutes and dilute with saturated aqueous sodium chloride.

- 5 Dry (sodium sulfate), filter and concentrate. Purify (silica gel chromatography using deactivated silica gel obtained by flushing with 3% (2 M ammonia/methanol) in dichloromethane), and elute with 10:90 to 100:0 ethyl acetate: hexanes) to give the desired compounds: (R)-3-benzyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol (2.08 g top spot), (R)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-
- 10 dimethylpropoxy)-1-methylethylamino]-propan-1-ol (1.79g bottom spot) and 3.4 g of mixed fractions.

MS (ES): $m/z = 396.5$ [M+H]

(2S,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methylmorpholine

- 15 2R,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methylmorpholine

- Add camphorsulfonic acid (1.69 g, 7.28 mmol) to (R)-3-benzyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol (1.60 g, 4.04 mmol) in toluene (65 mL) and heat to 100 °C for 1 hour. Cool to room temperature, dilute with ethyl acetate, wash with 2 N sodium hydroxide and saturated aqueous sodium chloride. Dry
- 20 (magnesium sulfate), filter and concentrate. Purify (silica gel chromatography using deactivated silica gel prepared as previously described, eluting with 10:90 to 70:30 ethyl acetate:hexanes) to give the desired compounds (2S,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methylmorpholine (490 mg, 39% top spot,) and (2R,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-
- 25 methylmorpholine (495mg, 40% bottom spot).

MS (ES): $m/z = 308.3$ [M+H]

(2R,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

- 30 Add N, N-diisopropylethylamine (0.41 g, 3.19 mmol) to (2R,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methylmorpholine (0.49 g, 1.59 mmol) and di-tert-butyl dicarbonate (1.04 g, 4.78 mmol) in dichloroethane (16 mL) at room

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temperature and heat to 70 °C for 12 hours. Cool to room temperature and concentrate. Dilute with ethyl acetate and wash with 1 N aqueous citric acid and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the desired compound as an oil.

MS (ES): m/z = 352.3 [M-tert-butyl]

(2R,3S,5S)-2-(2,2-Dimethylpropoxy)-5-hydroxymethyl-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Stir (2R,3S,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.65 g, 1.59 mmol) and 20% palladium hydroxide on carbon (0.65 g) in methanol (25 mL) under a hydrogen atmosphere at room temperature for 2 hours. Filter through Celite®, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes) to give the desired compound as an oil (471 mg 93.0%).

MS (ES): m/z = 340.3 [M+Na]

(2R,3S,5R)-2-(2,2-Dimethylpropoxy)-5-formyl-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Add pyridine sulfur trioxide complex (0.42 g) to (2R,3S,5S)-2-(2,2-dimethylpropoxy)-5-hydroxymethyl-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.46 g, 1.45 mmol) and N, N-diisopropylethylamine (0.66 g, 5.07 mmol) in dichloromethane (1 mL) and dimethylsulfoxide (4 mL) at -2° C and stir 30 minutes. TLC shows some alcohol remaining. Add more pyridine sulfur trioxide (100 mg) and stir 30 minutes. Pour into ice-cold saturated aqueous sodium chloride and extract with ethyl acetate. Wash the ethyl acetate layer with 1 N aqueous citric acid, saturated aqueous sodium chloride), dry (magnesium sulfate), filter and concentrate to give the title compound as an oil (456 mg).

Preparation 301

(R)-3-Benzoyloxy-2-[(R)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol
(R)-3-Benzoyloxy-2-[(S)-2,2-bis-(2,2-dimethylpropoxy)-1-methylethylamino]-propan-1-ol

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Add magnesium sulfate (30.23 g, 251.10 mmol) to (R)-2-amino-3-benzyloxypropan-1-ol (12.30 g, 67.87 mmol) and 1,1-bis-(2,2-dimethylpropoxy)-propan-2-one (23.45 g, 101.80 mmol) in tetrahydrofuran (100 mL) at room temperature and stir for 2 hours. Filter and concentrate. Dissolve in methanol (200 mL) and cool in an ice water bath. Add sodium cyanoborohydride (8.53 g, 135.73 mmol) and then acetic acid (4.08 g, 67.87 mmol) dropwise. Warm to room temperature, stir 2 hours and concentrate to ~ 50mL. Dilute with ethyl acetate (~200 mL) and add water (~50 ml) followed by 1 N sodium hydroxide (~200 mL). Stir 20 minutes and dilute with saturated aqueous sodium chloride. Dry (sodium sulfate), filter and concentrate to give the title compounds.

MS (ES): $m/z = 396.5$ [M+H]

Preparation 302

(2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

{(S)-2-benzyloxy-1-[1-(2,2-dimethylpropoxy)-2-iodoethoxymethyl]-ethyl}-carbamic acid tert-butyl ester

Add N-iodosuccinimide (14.19 g, 74.63 mmol) to ((R)-2-benzyloxy-1-hydroxymethylethyl)-carbamic acid tert-butyl ester (15.00 g, 53.30 mmol) and 2,2-dimethyl-1-vinyloxypropane (9.13 g, 79.96 mmol) in acetonitrile (267 mL) at room temperature. Heat to 60 °C under nitrogen for 2 hours. Cool to room temperature and dilute with ethyl acetate. Wash with water and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes) to give the desired compound as an oil (23.4 g 84.2%).

MS (ES) = 544.2 [M+Na]

(2R,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add sodium hydride (2.81 g, 70.27 mmol) to {(S)-2-benzyloxy-1-[1-(2,2-dimethylpropoxy)-2-iodoethoxymethyl]-ethyl}-carbamic acid tert-butyl ester (22.90 g, 43.92 mmol) in N,N-dimethylformamide (200 mL) at room temperature and heat to 55 °C for 1 hour. Cool to room temperature and pour into ethyl acetate and saturated aqueous

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ammonium chloride. Wash the organic layer with water, 10% aqueous potassium carbonate, 1 N citric acid, 1 N lithium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter, concentrate to ~20g of an orange oil and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes to give the desired compound as an oil (7.3g, 84.5%).

MS (ES) = 294.2 [M-BOC]

(2R,5S)-2-(2,2-Dimethylpropoxy)-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester

10 Stir (2R,5S)-5-benzyloxymethyl-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (7.05 g, 17.92 mmol) and 20 % palladium hydroxide on carbon in methanol (150 mL) under 1 atmosphere of hydrogen gas at room temperature for 12 hours. Filter and concentrate to give the desired compound as a thick oil which is used directly in the next step without further purification (5.10 g).

15 MS (ES) = 326.3 [M+Na]

(2R,5R)-2-(2,2-Dimethylpropoxy)-5-formylmorpholine-4-carboxylic acid tert-butyl ester

Add pyridine sulfur trioxide complex (4.82 g, 30.26 mmol) to (2R,5S)-2-(2,2-dimethylpropoxy)-5-hydroxymethylmorpholine-4-carboxylic acid tert-butyl ester (5.10 g, 16.81 mmol) and N, N-diisopropylethylamine (7.61 g, 58.83 mmol) in dimethylsulfoxide (42 mL) and dichloromethane (8 mL) at -4 °C. Stir 20 minutes, pour into ice cold saturated aqueous sodium chloride. Extract with 10% ethyl acetate/hexanes. Wash with 0.1 N aqueous citric acid and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate to give the desired compound of a colorless oil, which is used directly in the next step without further purification (5.02 g).

(2R,5R)-5-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

30 Add tetrabutylammonium fluoride (18.32 mL, 18.32 mmol, 1.0 M in tetrahydrofuran) to (2R,5R)-2-(2,2-dimethylpropoxy)-5-formylmorpholine-4-carboxylic acid tert-butyl ester (5.02 g, 16.66 mmol) and 1,3-difluoro-5-(2-nitroethyl)-benzene (3.43 g, 18.32 mmol) in tetrahydrofuran (28 mL) at -10 °C and stir 20 minutes. Pour into ice

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cold saturated aqueous sodium chloride and extract with ethyl acetate. Wash with 0.1 N aqueous citric acid and saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 20:80 to 30%:70 diethyl ether:hexanes) to give a mixture of 2 diastereomers (3.66 g, ~75:25 mixture) which are separated using chiral chromatography to give the desired compound (~2.45g, 34.0%).

MS (ES): $m/z = 487.3$ [M-H]

(2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add sodium borohydride (0.86 g, 22.60 mmol) to (2R,5R)-5-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-nitropropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (2.30 g, 4.71 mmol) and nickel (II) chloride (1.34 g, 10.36 mmol) in methanol (47 mL) at room temperature over ~2 minutes. Stir for 20 minutes, add water (~3 mL) and concentrate. Dilute with ethyl acetate (~75 mL), filter through Celite®, wash with 10% aqueous potassium carbonate, saturated aqueous sodium chloride, Dry (magnesium sulfate), filter and concentrate to give the title compound as an off-white solid (1.7 g, 78.7%).

MS (ES): $m/z = 459.2$ [M+H]

The compound of Preparation 303-305 may be prepared as a mixture of diastereomers essentially as described in Preparation 302 using 1-methyl-1-vinyloxymethylcyclopentane and 3-benzyloxyphenyl nitroethane.

| Prep | Compound | MS (ES) [M+H] |
|------|---|------------------|
| 303 | (2R,5R)-5-[2-Amino-3-(3-benzyloxy-phenyl)-1-hydroxy-propyl]-2-(1-methyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 555 |
| 304 | (2R,5R)-5-[2-Amino-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(cyclohexylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 485.3 |
| 305 | (2R,5R)-5-[2-Amino-3-(3,5-difluorophenyl)-1-hydroxy-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 459.3 |

Preparation 306

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(2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester
(R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-oxomorpholine-4-carboxylic acid tert-butyl ester

- 5 Add diisopropylethylamine (1 mL, 6.05 mmol) to a solution of (2R,3R,4S)-2-amino-3-benzyloxy-4-dibenzylamine-5-(3,5-difluorophenyl)-pentan-1-ol (1.02 g, 1.976 mmol) and phenyl bromoacetate (750 mg, 3.48 mmol) in N,N-dimethylformamide (30 mL) at room temperature. Stir the reaction mixture at room temperature overnight (~14h). Add di-tert-butyl dicarbonate (1 g, 4.58 mmol) and stir at room temperature for
- 10 20 h. Dilute with ethyl acetate, wash with 5% aqueous citric acid, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 2:98 ethyl acetate:hexanes), to give the desired compound as a white solid (1.05 g, 81%).
- MS (ES): $m/z = 657 [M+H]^+$

- 15 (R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-hydroxymorpholine-4-carboxylic acid tert-butyl ester

- Add diisobutylaluminum hydride (1.4 mL, 1.37 mmol, 1.0 M in toluene) to a solution of (R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-oxomorpholine-4-carboxylic acid tert-butyl ester (0.75 g, 1.1 mmol) in of dry toluene
- 20 (15 mL) at -78 °C under nitrogen and stir at this temperature for 2 hours (Monitor by TLC). Add methanol to quench the reaction (1.0 mL), then saturated aqueous potassium sodium tartrate (Rochelle salt) and ethyl acetate. Warm to room temperature and stir vigorously for 30 minutes. Separate the organic layer and extract the aqueous with ethyl acetate. Combine the organic layers and dry (magnesium sulfate), filter and concentrate to
- 25 give the desired compound as a mixture of the two possible isomers as a white solid and used in the next step without further purification (0.75 g).
- MS (ES): $m/z = 659 [M+H]^+$

Trifluoromethanesulfonic acid 2,2-dimethylpropyl ester

- 30 Add trifluoromethansulphonic anhydride (1.12 mL, 6.8 mmol) to a solution of neopentylalcohol (0.5 g, 5.7 mmol) and 2,6-lutidine (0.7 mL, 6.8 mmol) in dichloromethane (10 mL) at -78 °C and stir for 1 hour. Add water to quench the reaction,

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separate the organic layer and extract the aqueous layer with dichloromethane. Combine the organic layers, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 1:4 hexane:dichloromethane) to give the desired compound as an oil (0.9 g, 72% yield).

5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.03 (s, 9H), 1.18 (s, 2H)

(2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenylpropyl)]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add sodium hydride (16 mg, 0.4 mmol, 60% dispersion in mineral oil) to (R)-5-
10 [(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-hydroxymorpholine-4-carboxylic acid tert-butyl ester (175 mg, 0.3 mmol,) in dry dimethylformamide (1.0 mL) at 0 °C and stir for 10 min. Add trifluoromethanesulfonic acid 2,2-dimethylpropyl ester (90 mg, 0.4 mmol) in dry dimethylformamide (0.5 mL), warm slowly to room temperature and stir for 1 hour. Add water to quench the reaction
15 and extract the aqueous layer with diethyl ether. Combine the organic layers, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 90:10 hexanes:ethyl acetate) to give the desired compound as white solid (100 mg, 52% yield over two steps).

MS (ES): $m/z = 729$ $[\text{M}+\text{H}]^+$

20 (2R,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Stir (2R,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl) -
propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.1 g,
25 0.14 mmol) and 20% palladium hydroxide on carbon (0.1 g, 0.06 mmol, 60% moisture) in ethyl acetate (5 mL) under 1 atmosphere of hydrogen gas at room temperature overnight. Filter the suspension through a pad of filtering agent, wash with ethyl acetate and concentrate to give the title compound (0.06 g, 90%).

MS (ES): $m/z = 459$ $[\text{M}+\text{H}]^+$

30 Preparation 307

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester
(3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-one

- 5 Add 2(R)-trifluoromethanesulfonyloxypropionic acid methyl ester (6 g, 25.42 mmol) to a solution of (2R,3S,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3,5-difluorophenyl)-pentan-1-ol bishydrochloride (4.7 g, 7.94 mmol) and triethylamine (5 mL, 35.87 mmol) in dichloromethane (150 mL). Stir the reaction mixture at room temperature for 68 hours. Dilute with dichloromethane and wash with 5% aqueous citric acid, saturated aqueous sodium chloride, dry (magnesium sulfate), filter, concentrate and
10 purify (silica gel chromatography, eluting with 10:90 to 20:80 ethyl acetate:hexanes) to give the desired compound (2.93 g, 65%).

MS(ES): m/z = 571

- 15 (2RS,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-ol

- Add diisobutylaluminum hydride (2.48 mL, 2.48 mmol, 1.0 M in toluene) to a solution of (3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-one (1.09 g, 1.91 mmol) in dry toluene (20 mL) at -78 °C
20 under nitrogen and stir at this temperature for 15 minutes. Quench by adding methanol (1.0 mL). Add saturated aqueous potassium sodium tartrate (Rochelle salt) and ethyl acetate, warm to room temperature and stir vigorously for 30 minutes. Separate the organic layer and extract the aqueous with ethyl acetate. Combine the organic layers, dry (magnesium sulfate), filter and concentrate to give the desired compound as a mixture of
25 the two possible epimers as a white solid which is used directly in the next step without further purification (1.08 g, 99% yield).

MS(ES): m/z = 573

- 30 Dibenzyl-[(1S,2S)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl]-amine

 Mix (3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-ol (1.06 g, 1.85 mmol) with neopentanol (1.63g, 18.5

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mmol,) in dichloromethane (0.2 mL). Add 4 Å molecular sieves (850 mg), then methanesulphonic acid (2.4 mL, 37 mmol) and heat at 50 °C for 4 hours. Cool to room temperature, dilute with dichloromethane and add slowly to a solution of saturated aqueous sodium bicarbonate. Extract the aqueous layer with dichloromethane, dry
5 (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 100:0 to 90:10 hexanes:ethyl acetate) to give the desired compound as a white solid (665 mg, 56% yield).

MS(ES): m/z = 643

10 (2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Add di-tert-butyl dicarbonate (683 mg, 3.03 mmol) to a solution of dibenzyl-
{(1S,2S)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-ethyl}-amine (650 mg, 1.01 mmol) and diisopropylethylamine
15 (353 mL, 2.02 mmol) in 1,2-dichloroethane (11 mL) and stir at 75 °C for 6 hours. Concentrate and purify (silica gel chromatography, eluting with 80:20 to 0:100 hexanes:dichloromethane) to give the desired compound as a white solid (650 mg, 87 % yield).

MS(ES): m/z = 743

20

(2R,3S,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Stir (2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester
25 (645 mg, 0.87 mmol) and 20% palladium hydroxide on carbon (60% moisture, 645 mg) in ethyl acetate (10 mL) under one atmosphere of hydrogen gas at room temperature overnight. Filter the suspension through a pad of filtering agent, wash with ethyl acetate and concentrate to give the desired compound (400 mg, 97%).

MS(ES): m/z = 473

30

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

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Add acetic anhydride (0.084 ml, 0.89 mmol) to a solution of (2R,3S,5R)-5-
 [(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-
 methylmorpholine-4-carboxylic acid *tert*-butyl ester (400 mg, 0.85 mmol) in dry
 dichloromethane (9 mL). Add triethylamine (0.179 mL, 1.27 mmol), stir 1 hour at room
 5 temperature, concentrate and purify (silica gel cartridge chromatography, eluting with 1:1
 hexanes:ethyl acetate) to give the title compound as a white solid (397 mg, 91%).
 MS(ES): $m/z = 515$ [$M^+ + H$]

The compounds of Preparation 308-332 may be prepared essentially as described
 10 in Preparation 307:

| Prep | Compound | MS (ES) [M+H] |
|------|--|------------------|
| 308 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylbutoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 529 |
| 309 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 441 [M-BOC+H] |
| 310 | 2R,3S,5R)-5-[(1S,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-(2-methoxyacetylamino)-propyl]-2-(2,2-dimethylbutoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 503 [M-BOC+H] |
| 311 | (2R,3S,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(3-methoxypropionylamino)-propyl]-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | |
| 312 | (2R,3S,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-1-hydroxy-2-(2-methoxyacetylamino)-propyl]-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 471 [M-BOC+H] |
| 313 | (2R,3S,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-2-(cyclopropane-carbonylamino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 467 [M-BOC+H] |
| 314 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(bicyclo[2.1.1]hex-5-ylmethoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester-Isomer 1 | 439 [M-BOC+H] |
| 315 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(bicyclo[2.1.1]hex-5-ylmethoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester-Isomer 2 | 439 [M-BOC+H] |
| 316* | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(4,4-difluorocyclohexylmethoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 477 [M-BOC+H] |
| 317 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-difluoro-2,2-dimethylbutoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | |

| | | |
|-------|---|------------------------------|
| 318 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3-fluoropropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 527 [M+Na] |
| 319 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methyl-2-(3,3,3-trifluoropropoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 541 [M+H] |
| 320 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-ethylbutoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 573 [M+HCO ₂] |
| 321 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methyl-2-(tetrahydropyran-4-ylmethoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 565 [M+Na] |
| 322 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methyl-2-(4,4,4-trifluorobutoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 577 [M+Na] |
| 323** | (2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-fluorocyclohexylmethoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 459 |
| 324 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methyl-2-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 527 [M+H-tBu] |
| 325 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-3-methyl-2-((S)-2-methyl-butoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 515.5 [M ⁺] |
| 326 | (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 581 [M+Na] |
| 327 | (2R, 3S, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-methyl-2-(1-trifluoromethylcyclopropyl)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 589 [M+Na] |
| 328 | (2R, 3S, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-difluoro-2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 573 [M+Na] |
| 329 | (2R, 3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(1-difluoromethyl-cyclopentylmethoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 621 [M+HCO ₂] |
| 330 | (2R, 3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-bis-fluoromethyl-butoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 609 [M+HCO ₂] |
| 331 | (2R,3S,5R)-5-[(1S,2S)-[2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-cyclopentylmethoxy-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 471 [M+H-t-Bu] |

*Glycosidation step may be performed as described in Preparation 306.

**Glycosidation step may be performed as described in Preparation 351.

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Preparation 332

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-ethylmorpholine-4-carboxylic acid tert-butyl ester
(3S,5R)-5-[(1S,2S)-1-benzyl-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-ethyl-2-oxomorpholine-4-carboxylic acid tert-butyl ester

- Slowly add lithium hexamethyldisilazide (2.28 mL, 2.28 mmol, 1.0 M in tetrahydrofuran) at -78°C under nitrogen to a solution of (R)-5-[(1S,2S)-1-benzyl-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-oxomorpholine-4-carboxylic acid tert-butyl ester (1 g, 1.52 mmol) and iodoethane (1.24 mL, 15.2 mmol) in anhydrous tetrahydrofuran (10 mL). Stir at -78°C for 45 minutes, remove the bath and stir for 1.5 hours. Add water and ethyl acetate. Separate the organic layer and extract the aqueous layer with ethyl acetate. Combine the organic layers, dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 90:10 hexane:ethyl acetate) to give the desired compound as a white solid (848 mg, 82%).
- MS(ES): $m/z = 685$

(2R,3S,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-ethylmorpholine-4-carboxylic acid tert-butyl ester

- Prepare (2R,3S,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-ethylmorpholine-4-carboxylic acid tert-butyl ester essentially as described for the preparation of (2R,3S,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester.
- MS(ES): $m/z = 487$

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-ethylmorpholine-4-carboxylic acid tert-butyl ester

- Prepare (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-ethylmorpholine-4-carboxylic acid tert-butyl ester essentially as described for the preparation of (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester.

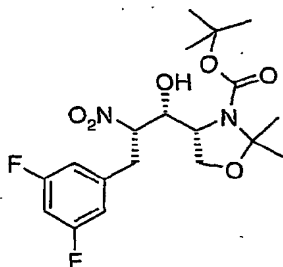
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MS(ES): $m/z = 429$ [M^+ -BOC]

The compounds of Preparations 333-334 may be prepared essentially as described in Preparation 332. In Preparation 335 the corresponding triflate may be used as the alkylating agent with potassium hexamethyldisilazane as the base.

| Prep | Compound | MS(ES) [M+H] |
|------|---|------------------------------|
| 333 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-3-butyl-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 579 [M+Na] |
| 334 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxydimethylpropoxy]-3-(3-fluoropropyl)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 356 [M+HCO ₂] |

Preparation 335



(R)-4-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester

(S)-4-Formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester

Add dropwise over 2 hours a solution of pyridine sulfur trioxide (390 g, 2452.83 mmol) in dimethylsulfoxide (1600 mL) to a 6 °C maintained solution of (S)-4-

hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (350 g,

1515.15 mmol) in diisopropylethylamine (1225 mL) with a dimethylsulfide trap. Over 30 minutes add water (1050 mL) keeping temperature below 15 °C. Stir at 15 °C for 1.5

hours under a stream of nitrogen. Extract with ethyl acetate (5 L), wash with 5% aqueous citric acid (2 x 1.5 L), saturated aqueous sodium chloride (2 x 1.5 L), dry (magnesium sulfate), filter, and concentrate to give the desired compound which is used in the next

reaction without further purification (365 g).

MS (ES): $m/z = 230$ [M+H]

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(R)-4-[(1R,2S)-3-(3,5-Difluorophenyl)-1-hydroxy-2-nitropropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Add tetrabutylammonium fluoride in 5 minutes (50 mL, 50 mmol, 1.0 M solution in tetrahydrofuran) to a solution of (S)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (200 g, 873.362 mmol) and 1,3-difluoro-5-(2-nitroethyl)-benzene (164 g, 877.005 mmol) in tetrahydrofuran (1.2 L) at 8 °C. Allow to warm to room temperature and stir for 14 hours. Partition between ethyl acetate (4 L) and saturated aqueous sodium chloride (1.5 L). Wash the organic layer with saturated aqueous ammonium chloride, saturated aqueous sodium chloride, water, dry (magnesium sulfate), filter and concentrate to give 379 g of a crude waxy pale orange solid. Recrystallize in dichloromethane/hexanes to give the title compound (137.15 g, 37.7%).
MS (ES): $m/z = 417$ [M+H]

15

Preparation 336

(R)-4-[(1S,2S)-1-Benzoyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

(R)-4-[(1S,2S)-2-Dibenzylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

Add benzyl bromide (75 mL, 630.55 mmol) to a suspension of potassium carbonate (85 g, 615.006 mmol) and (R)-4-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (80 g, 207.25 mmol) in acetonitrile (900 mL). Heat to reflux for ~16 hours, cool to room temperature, and dilute with ethyl acetate (2 L). Wash with ammonium chloride (1.5 L), saturated aqueous sodium chloride (1.5 L), dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 5:95 to 20:80 ethyl acetate:hexanes) to give the desired compound as a white solid (102.1 g, 87%).
MS (ES): $m/z = 567$ [M+H]

30

(R)-4-[(1S,2S)-1-benzoyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

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- Add sodium hydride (4.4 g, 110 mmol, 60% in mineral oil) portionwise to a room temperature maintained solution of (R)-4-[(1S,2S)-2-dibenzylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (50.5 g, 89.222 mmol) and benzyl bromide (22 mL, 184.96 mmol) in N,N-dimethylformamide (400 mL). Stir for 15 minutes and pour into saturated aqueous ammonium chloride. Extract with ethyl acetate, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 2:98 to 4:96 ethyl acetate:hexanes) to give the title compound as a viscous oil that solidifies upon standing (48.5 g, 83%).
- MS (ES): $m/z = 657$ [M+H]

Preparation 337

- (2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester
- Trifluoromethanesulfonic acid 2-fluoro-2-methylpropyl ester
- Add trifluoromethanesulphonic anhydride (4.3 mL, 26.0 mmol) to a solution of 2-fluoro-2-methylpropan-1-ol (2.0 g, 21.7 mmol) and 2,6-lutidine (3.0 mL, 26.0 mmol) in dichloromethane (25 mL) at -78°C . Warm slowly to room temperature and stir at room temperature for 1 hour. Add water to quench the reaction, separate the organic layer and extract the aqueous layer with dichloromethane. Combine the organic layers, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with dichloromethane), to give the desired compound as an oil (3.4 g, 70% yield).
- $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.46 (d, $J = 21$ Hz, 6H) and 4.41 (d, $J = 18.6$ Hz, 2H)

- (2S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)propyl]-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester
- Add sodium hydride (0.09 g, 2.28 mmol, 60% dispersion in mineral oil) to (R)-5-[1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-hydroxymorpholine-4-carboxylic acid tert-butyl ester (1.0g, 1.52 mmol,) in dry N,N-dimethylformamide (12.0 mL) at room temperature and stir for 15 min. Add trifluoromethanesulfonic acid 2-fluoro-2-methylpropyl ester (0.05 g, 2.28 mmol) in dry N,N-dimethylformamide (2 mL), and stir for 1 hour. Add water to quench the reaction and extract the aqueous layer with

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diethyl ether. Combine the organic layers, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 100:0 to 60:40 hexanes:ethyl acetate), to give the desired compound as white solid (0.68 g, 62% yield over two steps).

MS (ES): $m/z = 733$ $[M+H]^+$

5

(2S,5R)-5-[(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Stir (2S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenylpropyl)-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.68 g, 0.93 mmol) and 20% palladium hydroxide on carbon (0.68 g, 0.60 mmol, 60% moisture) in ethyl acetate (25 mL) under 1 atmosphere of hydrogen gas at room temperature overnight. Filter the suspension through a pad of filtering agent, wash with ethyl acetate and concentrate to give the desired compound (0.40 g, 93%).

MS (ES): $m/z = 463$ $[M+H]^+$

15

(2S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add acetic anhydride (0.084 mL, 0.91 mmol) to a solution of (2S,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2-fluoro-2-methylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (400 mg, 0.86 mmol) and triethylamine (0.81 mL, 130 mmol) in dry dichloromethane (10 mL) at room temperature and stir for 4 hours, concentrate and purify (silica gel cartridge chromatography, eluting with 2:1 to 1:2 hexanes:ethyl acetate), to give the desired compound as a white solid (0.37 g, 80%).

MS (ES): $m/z = 505$ $[M+H]^+$

25

The compounds of Preparations 338–342 may be prepared essentially as described in Preparation 337.

| Prep | Compound | MS (ES) |
|------|--|---------------|
| 338 | (2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 567 [M+Na] |
| 339 | (2R, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(1-difluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 585 [M+Na] |

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| | | |
|-----|---|---------------------------|
| 340 | (2R, 5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(1-fluoro-cyclopentylmethoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 575 [M+HCO ₂] |
| 341 | (2R, 5R)-5-[(1S,2S)-2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-bis-fluoromethyl-butoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 595 [M+HCO ₂] |
| 342 | (2R,5R)-5-[(1S,2S)-[2-Acetylamino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 569 [M+H] |

Preparation 343

3-Propylsulfanylbenzaldehyde

Reflux a suspension of potassium carbonate (22.4 g), 1-iodopropane (10.3 mL) and 3-bromothiophenol (8.4 mL) in acetone (375 mL) for 5 hours. Cool to room temperature, filter through diatomaceous earth, and concentrate. Dissolve the residue in hexanes, filter through a silica gel plug, and concentrate to give 1-bromo-3-propyl-sulfanylbene (18 g, 95%) as an oil (GC-MS: $m/z = 231$). Add this material (12 g) to a solution of *n*-butyllithium (57 mmol) in THF (50 mL) at -78°C . Stir for 45 min, add N,N-dimethylformamide (8.1 mL) and warm to room temperature. Stir for 15 min, pour into water (175 mL), and extract into diethyl ether (3 x 200 mL). Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography) to give the title compound (7.3g, 92%).

GC-MS: $m/z = 180$

15

The compound of Preparation 344 may be prepared essentially as described in Preparation 343.

| Prep | Compound |
|------|--------------------------------|
| 344 | 3-Isobutylsulfanylbenzaldehyde |

Preparation 345

20

3-Fluoro-5-propylsulfanylbenzaldehyde

Dissolve sodium propanethiolate (7.5g) in DMF (250mL) at ambient temperature, then chill to -30°C and add 1-bromo-3,5-difluorobenzene (8.35 mL). After 1 hour, warm to -15°C , and stir for an additional 3 hours. Pour into water (2 L) and extract into hexanes (3 X 500 mL). Wash the resulting organic solution with saturated aqueous

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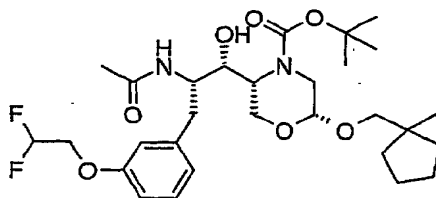
sodium chloride (100 mL), dry (magnesium sulfate), filter and concentrate. Filter through a plug of silica gel, wash with 10:90 ethyl acetate:hexanes and concentrate to give 1-bromo-3-fluoro-5-propylsulfanylbenzene (16.2 g, 90%). The title compound is prepared essentially as described in Preparation 343.

5

The compound of Preparation 346 may be prepared essentially as described in Preparation 345.

| Prep | Compound |
|------|---|
| 346 | 3-Fluoro-5-isobutylsulfanylbenzaldehyde |

Preparation 347



10

(2R,5R)-5-((1S,2S)-2-Acetylamino-3-[3-(2,2-difluoroethoxy)-phenyl]-1-hydroxypropyl)-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester
 (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-benzyloxyphenyl)-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

15

Add acetyl chloride (0.13 mL, 1.82 mmol) to an ice cold solution of (2R,5R)-5-[2-amino-3-(3-benzyloxyphenyl)-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.91 g, 1.652 mmol) and N,N-diisopropylethylamine (0.58 mL, 3.30 mmol) in dichloromethane (20 mL). Stir 15 minutes and dilute with ethyl acetate and wash with 1 N hydrochloric acid, saturated aqueous sodium chloride, dry (magnesium sulfate) and purify (silica gel chromatography, elutin with dichloromethane/ethyl acetate) to give the desired compound (246 mg).

20

MS (ES): $m/z = 597$ [M+H]

25

(2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

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Hydrogenate (2R,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-benzyloxyphenyl)-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester (244 mg) in methanol (15 mL) with 20% palladium hydroxide on carbon (26 mg) at 50 psi hydrogen for 18 hours. Filter and concentrate to give the desired compound (204 mg). MS (ES): m/z = 507 [M+H]

(2R,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2,2-difluoroethoxy)-phenyl]-1-hydroxypropyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

Dissolve (2R,5R)-5-[(1S,2S)-2-acetylamino-1-hydroxy-3-(3-hydroxyphenyl)-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester (204 mg) and 2,2-difluoro-1-bromoethane (0.065 mL) and cesium carbonate (391 mg) in N,N-dimethylformamide (5 mL) and heat to 60 °C for 18 hours. Dilute with ethyl acetate, wash with saturated aqueous sodium chloride, dry and purify (silica gel chromatography, eluting with 1:1 ethyl acetate:dichloromethane), to give the desired compound (223 mg). MS (ES): m/z = 593 [M+Na]

The compounds of Preparations 348-350 may be prepared essentially as described in Preparation 347.

| Prep | Compound | MS (ES) [M+H] |
|------|---|------------------|
| 348 | (2R,5R)-5-[(1S,2S)-1-Acetoxy-2-acetylamino-3-[3-(2,2-difluoroethoxy)-phenyl]-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 635 [M+Na] |
| 349 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-propoxyphenyl)-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 571 [M+Na] |
| 350 | (2R,5R)-5-[(1S,2S)-1-Acetoxy-2-acetylamino-3-(3-propoxyphenyl)-propyl]-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 613 [M+Na] |

20

Preparation 351

Dibenzyl-[(1S,2R)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6S)-6-(1-fluorocyclohexylmethoxy)-5-methylmorpholin-3-yl]-ethyl]-amine

Add triphosgene (246 mg, 0.79 mmol) at room temperature to a solution of (3S,5R)-5-[(1R,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-

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methyldmorpholin-2-ol (1 g, 1.75 mmol) and triethylamine (0.99 mL, 7 mmol) in anhydrous dichloromethane (17 mL). Stir for 30 min, cool to 0 °C and add (1-fluorocyclohexyl)-methanol (1.16g, 8.75 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.64 mL, 3.5 mmol). Stir at 0 °C for 1 hour and at room temperature for 2 hours. Add more trimethylsilyl trifluoromethanesulfonate (0.16 mL, 0.87 mmol) and stir at room temperature for 30 min. Add 10% aqueous potassium carbonate, separate the organic layer and extract the aqueous layer with dichloromethane. Combine the organic layers, dry (sodium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 hexanes:ethyl acetate), to give the title compound as a colorless oil (375 mg).

MS (ES): m/z = 687 [M+H]

Preparation 352

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(2-ethylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester
1-Ethyl-2-(2-nitroethyl)-benzene

Dissolve 2-ethyl benzaldehyde (7 mL, 53.2 mmol); nitromethane (8.5 mL, 158 mmol), and ammonium acetate (1.6 g, 20.8 mmol) in acetic acid (40 mL) and heat to reflux under a nitrogen atmosphere for 17 hours. Cool to room temperature and concentrate. Dissolve in isopropyl alcohol (150 mL) and chloroform (750 mL) and add silica gel (108 g). To the resulting slurry, slowly add sodium borohydride (7.8 g, 206 mmol). Stir the mixture for 17 hours, filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 10:90 ethyl acetate:hexanes), to give the desired compound as an orange oil.

¹HNMR (400 MHz, CDCl₃) δ 7.12-7.26 (m, 4 H), 4.57 (t, J = 8.0 Hz, 2H), 3.67 (t, J = 8.0 Hz, 2H), 2.68 (q, J = 8.0 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H)

(2R,3S,5R)-2-(2,2-Dimethylpropoxy)-5-[(1R,2S)-3-(2-ethylphenyl)-1-hydroxy-2-nitropropyl]-3-methylmorpholine-4-carboxylic acid tert-butyl ester

To a 0 °C solution of 1-ethyl-2-(2-nitroethyl)-benzene (430 mg, 2.40 mmol) and (2R,3S,4R)-2-(2,2-dimethylpropoxy)-5-formyl-3-methylmorpholine-4-carboxylic acid tert-butyl ester (565 mg, 1.79 mmol) in dry tetrahydrofuran (10 mL) add tetrabutyl-

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ammonium fluoride (1.6 mL, 1.6 mmol, 1.0 M in tetrahydrofuran). After 30 minutes, pour into ethyl ether and wash with saturated aqueous sodium chloride followed by water (3x) and saturated aqueous sodium chloride again. Dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 0:100 to 20:80 ethyl acetate:hexanes), to give an inseparable mixture of aldol product diastereomers

MS (ES): $m/z = 493.2$ [M-H]

(2R,3S,5R)-5-[(1S,2S)-2-Amino-3-(2-ethylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve the mixture of diastereomers from the previous reaction containing (2R,3S,5R)-2-(2,2-dimethylpropoxy)-5-[(1R,2S)-3-(2-ethylphenyl)-1-hydroxy-2-nitropropyl]-3-methylmorpholine-4-carboxylic acid tert-butyl ester in dry methanol (12 mL) and add nickel (II) chloride (267 mg, 2.06 mmol). To the resulting suspension, add sodium borohydride (284 mg, 7.5 mmol) portion-wise over 1 minute. After 30 minutes, quench with water and reduce the volume on the rotary evaporator. Add more water and saturated aqueous sodium chloride. Extract with ethyl acetate. Combine the extracts, dry (sodium sulfate), filter and concentrate to give a diastereomeric mixture of amines containing the desired compound as a light brown oil (418 mg, 85%).

MS (ES): $m/z = 465.5$ [M+H]

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(2-ethylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Dissolve the diastereomeric mixture of amines from the previous reaction which contains (2R,3S,5R)-5-[(1S,2S)-2-amino-3-(2-ethylphenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (418 mg, 0.9 mmol) in dry dichloromethane (7 mL) under a nitrogen atmosphere and add acetic anhydride (90 μ L, 0.95 mmol) and triethylamine (150 μ L, 1.1 mmol). After 4 hours quench with methanol, concentrate and purify (silica gel chromatography) to give a mixture of amide diastereomers containing the title compound (243 mg). Purify the resulting mixture by HPLC, eluting with 65:35 acetonitrile:water with 8 μ M hydrochloric acid, to give the title compound as a single diastereomer (47 mg, 10% overall).

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MS (ES): $m/z = 529.3$ [M+Na]

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(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester
5 3-bromo-5-fluoro-phenol

Add aluminum chloride (13.51 g, 101.38 mmol) to 1-benzyloxy-3-bromo-5-fluoro-benzene (9.50 g, 33.79 mmol, prepared according to WO 03/101956) and dimethylaniline (40.96 g, 337.92 mmol) in dichloromethane (84 mL) at $\sim 0^\circ\text{C}$ under
10 nitrogen and stir 10 minutes. Remove ice-bath and stir 2 hours. Add 60 mL 2N hydrochloric acid dropwise. Separate layers and wash the organic layer with 2N hydrochloric acid (4x50mL). Extract the organic layer with 3N potassium hydroxide (4x50mL). Acidify with 5N hydrochloric acid and extract with dichloromethane (3x50mL). Dry the dichloromethane layer (sodium sulfate) and concentrate to give 4.3 g
15 (66.6%) of the desired compound as an oil.

1-bromo-3-fluoro-5-propoxy-benzene

Add propyl iodide (5.74 g, 33.77 mmol) to 3-bromo-5-fluoro-phenol (4.30 g, 22.51 mmol) and cesium carbonate (11.00 g, 33.77 mmol) in N,N-dimethylformamide
20 (75 mL) and stir at room temperature 1 hour, then heat at 50°C for 1 hour. Cool to room temperature and dilute with hexanes. Wash (water, 1N lithium chloride, saturated aqueous sodium chloride), dry (magnesium sulfate), filter and concentrate to give the desired compound as a colorless oil, 4.40 g (83.8 %).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.85-6.80 (m, 2H), 6.55 (dt, 1H, $J=6.4, 3.5$ Hz), 3.88 (t, 2H, $J=6.6$ Hz), 1.84-1.75 (m, 2H), 1.02 (t, 3H, $J=7.5$ Hz).
25

3-Fluoro-5-propoxy-benzaldehyde

Add n-butyl lithium (13 mL, 1.6M, 20.76 mmol) to 1-bromo-3-fluoro-5-propoxy-benzene (4.40 g, 18.88 mmol) in tetrahydrofuran (100 mL) cooled in a dry ice/acetone
30 bath over ~ 45 minutes, maintaining the internal temperature $< -70^\circ$. Stir 30 minutes and add N,N-dimethylformamide (2.76 g, 37.75 mmol). Stir 30 minutes and remove cold bath. After 1 hour, quench with saturated aqueous ammonium chloride. Wash organic

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layer with water and saturated aqueous sodium chloride. Dry (sodium sulfate), filter and concentrate to an oil. Purify on 120g silica gel eluting with 0 to 10% ethyl acetate in hexanes to give 2.26 g (65.7%) of the desired compound as an oil.

¹H-NMR (400 MHz, CDCl₃) δ 9.93 (d, 1H, J=1.8 Hz), 7.22-7.21 (m, 1H), 7.18-7.15 (m, 1H), 6.88 (dt, 1H, J=6.3, 3.4 Hz), 3.99 (t, 2H, J=6.6 Hz), 1.90-1.81 (m, 2H), 1.07 (t, 3H, J=7.5 Hz).

1-Fluoro-3-((E)-2-nitro-vinyl)-5-propoxy-benzene

Add ammonium acetate (2.63 g, 34.08 mmol) to 3-fluoro-5-propoxy-benzaldehyde (2.25 g, 12.35 mmol) and nitromethane (3.09 g, 50.63 mmol) in acetic acid (41 mL) at room temperature and heat in 140 °C oil bath for 3 hours. Cool to room temperature and pour into water. Extract with ethyl acetate, dry over magnesium sulfate, filter and concentrate to afford 1.94 g (69.8%) of the desired compound as an oil.

¹H-NMR (400 MHz, CDCl₃) δ 7.9 (d, 1H, J=13.6 Hz), 7.52 (d, 1H, J=13.6 Hz), 6.85-6.81 (m, 2H), 6.73 (dt, 1H, J=6.4, 3.5 Hz), 3.93 (t, 2H, J=6.4 Hz), 1.87-1.78 (m, 2H), 1.05 (t, 3H, J=7.5 Hz).

1-Fluoro-3-(2-nitro-ethyl)-5-propoxy-benzene

Add sodium borohydride (1.30 g, 34.46 mmol) to 1-fluoro-3-((E)-2-nitro-vinyl)-5-propoxy-benzene (1.94 g, 8.61 mmol) and silica gel (17 g) in chloroform (86 mL) and isopropanol (25 mL) at room temperature in portions over 5 minutes. Stir at room temperature 2 hours and filter. Concentrate the filtrate and dissolve in ethyl acetate. Wash with water and saturated aqueous sodium chloride, dry over magnesium sulfate, filter and concentrate. Purify on 40 g silica gel eluting with 100:0 to 70:30 hexanes:ethyl acetate to give 1.1 g (56.2%) of the desired compound as an oil.

¹H-NMR (400 MHz, CDCl₃) δ 6.53-6.47 (m, 3H), 4.59 (t, 2H, J=7.3 Hz), 3.88 (t, 2H, J=6.6 Hz), 3.26 (t, 2H, J=7.5 Hz), 1.84-1.75 (m, 2H), 1.03 (t, 3H, J=7.5 Hz).

(2R,3S,5R)-2-(2,2-Dimethyl-propoxy)-5-[3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-2-nitro-propyl]-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

Add tetrabutyl ammonium fluoride (2 mL, 1.0 M in tetrahydrofuran, 2.15 mmol) to (2R,3S,5R)-2-(2,2-dimethyl-propoxy)-5-formyl-3-methyl-morpholine-4-carboxylic

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acid *tert*-butyl ester (0.61 g, 1.94 mmol) and 1-fluoro-3-(2-nitro-ethyl)-5-propoxy-benzene (0.48 g, 2.13 mmol) in tetrahydrofuran (4 mL) at $\sim 10^{\circ}\text{C}$ and stir 30 minutes. Pour into ice-cold saturated aqueous sodium chloride and separate the layers. Wash the organic layer with saturated aqueous ammonium chloride and saturated aqueous sodium chloride. Dry over magnesium sulfate, filter and concentrate to an oil. Purify on 80 g silica gel eluting with 100:0 to 50:50 hexanes:diethyl ether to give 0.683 g (65%) of the desired compound as a mixture of 2 major and 1 minor diastereomers.

MS(ES): $m/z = 541.3$.

10 (2R,3S,5R)-5-[2-Amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid *tert*-butyl ester

Add sodium borohydride (0.11 g, 2.92 mmol) to (2R,3S,5R)-2-(2,2-dimethyl-propoxy)-5-[3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-2-nitro-propyl]-3-methyl-morpholine-4-carboxylic acid *tert*-butyl ester (0.36 g, 0.66 mmol) and nickel chloride (0.14 g, 1.06 mmol) in methanol (7 mL) at room temperature and stir 30 minutes. Add water (0.7 mL) and concentrate. Dilute with ethyl acetate and filter through celite. Wash (10 % potassium carbonate and saturated aqueous sodium chloride), dry (magnesium sulfate), filter and concentrate to give 0.340 g (100%) of the desired compound as a white solid.

20 MS(ES): $m/z = 513.5$.

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid *tert*-butyl ester

Add acetic anhydride (0.07 g, 0.70 mmol) to (2R,3S,5R)-5-[2-Amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid *tert*-butyl ester (0.34 g, 0.66 mmol) and triethylamine (0.10 g, 0.99 mmol) in tetrahydrofuran (6 mL) at room temperature and stir 1 hour. Dilute with ethyl acetate and wash with saturated aqueous ammonium chloride and saturated aqueous sodium chloride. Dry over magnesium sulfate, filter and concentrate. Purify on 12 g silica gel eluting with 100:0 to 20:80 hexanes:ethyl acetate to give 0.175 g of the desired compound as an oil.

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Preparation 354

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid *tert*-butyl ester
3-benzyloxy-5-fluoro-benzaldehyde

- 5 Add *n*-butyl lithium (35 mL, 1.6M, 55.96 mmol) over ~15 minutes to 1-bromo-3-fluoro-5-benzyloxy-benzene (14.30 g, 50.87 mmol) in tetrahydrofuran (300 mL) cooled in a dry ice/acetone bath, maintaining the internal temperature <-70 °. Stir 30 minutes and add N,N-dimethylformamide (7.44 g, 101.74 mmol). Stir 30 minutes and remove cold bath. After 1 hour, quench with saturated aqueous ammonium chloride. Wash
10 organic layer with water and saturated aqueous sodium chloride. Dry (sodium sulfate), filter and concentrate to an oil. Purify on 120 g silica gel eluting with 100:0 to 90:10 hexanes:ethyl acetate to give 3.75 g (32%) of the desired compound as an oil.
¹H-NMR (400 MHz, CDCl₃) δ 9.91 (d, 1H, J=0.9 Hz), 7.45-7.33 (m, 5H), 7.29 (s, 1H), 7.18 (d, 1H, J=7.9 Hz), 6.95 (dt, 1H, J=6.2, 3.5 Hz), 5.12 (s, 2H).

- 15 1-benzyloxy-3-fluoro-5-((E)-2-nitro-vinyl)-benzene

- Heat 3-benzyloxy-5-fluoro-benzaldehyde (3.75 g, 16.29 mmol), nitromethane (4.08 g, 66.79 mmol), and ammonium acetate (3.47 g, 44.96 mmol) in acetic acid (54 mL) in 125 °C oil bath under nitrogen for 4 hours. Cool to room temperature and pour
20 into ice/water. Extract with hexanes/ethyl acetate. Dry (magnesium sulfate), filter and concentrate. Purify on 120 g silica gel eluting with 100:0 to 80:20 hexanes:ethyl acetate to give 3.05 g (68.5%) of the desired compound as a yellow oil.
¹H-NMR (400 MHz, CDCl₃) δ 7.89 (d, 1H, J=14.1 Hz), 7.51 (d, 1H, J=13.6 Hz), 7.43-7.34 (m, 5H), 6.92 (s, 1H), 6.87-6.80 (m, 2H), 5.09 (s, 2H).

- 25 1-benzyloxy-3-fluoro-5-(2-nitro-ethyl)-benzene

- Add sodium borohydride (1.69 g, 44.64 mmol) to 1-benzyloxy-3-fluoro-5-((E)-2-nitro-vinyl)-benzene (3.05 g, 11.16 mmol) and silica gel (22g) in chloroform (112 mL) and isopropanol (33 mL) at room temperature in portions over 5 minutes. Stir at room
30 temperature 90 minutes and filter. Concentrate and dissolve in ethyl acetate. Wash (10% potassium carbonate and saturated aqueous sodium chloride), dry over magnesium

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sulfate, filter and concentrate. Purify on 120 g silica gel eluting with 100:0 to 80:20 hexanes:ethyl acetate to afford 1.33 g (43.3%) of the desired compound as an oil.

¹H-NMR (400 MHz, CDCl₃) δ 7.42-7.32 (m, 5H), 6.62-6.58 (m, 2H), 6.53 (dt, 1H, J=5.3, 3.1 Hz), 5.03 (s, 2H), 4.59 (t, 2H, J=7.3 Hz), 3.27 (t, 2H, J=7.3 Hz).

5

(2R,3S,5R)-5-[3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-2-nitro-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

Add tetrabutyl ammonium fluoride (14 mL, 1.0M in tetrahydrofuran, 14.30 mmol) to (2R,3S,5R)-2-(2,2-dimethyl-propoxy)-5-formyl-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (4.06 g, 12.88 mmol) and 1-Benzyloxy-3-fluoro-5-(2-nitro-ethyl)-benzene (3.90 g, 14.17 mmol) in tetrahydrofuran (26 mL) at ~-10 °C and stir 30 minutes. Pour into ice-cold saturated aqueous sodium chloride and separate the layers. Wash the organic layer with saturated aqueous ammonium chloride and saturated aqueous sodium chloride. Dry over magnesium sulfate, filter and concentrate to an oil. Purify on 330g silica gel eluting with 100:0 to 50:50 hexanes:diethyl ether to give 5.89 g (77.4%) of the desired compound as a mixture of 2 major and 1 minor diastereomers. MS(ES): *m/z* = 589.3.

20 (2R,3S,5R)-5-[2-Amino-3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

Add sodium borohydride (1.66 g, 43.87 mmol) to (2R,3S,5R)-5-[(1R,2S)-3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-2-nitro-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (5.89 g, 9.97 mmol) and nickel chloride (2.07 g, 15.95 mmol) in methanol (100 mL) at room temperature and stir 30 minutes. Add water (~10 mL) and concentrate. Dilute with ethyl acetate and filter through celite. Partition between ethyl acetate and saturated aqueous sodium chloride. Wash the organic layer with saturated aqueous sodium chloride, dry (sodium sulfate), filter and concentrate to give 4.32 g (77.3%) of the desired compound as a white solid. MS(ES): *m/z* = 561.3.

30

(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

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Add acetic anhydride (0.83 g, 8.09 mmol) to (2R,3S,5R)-5-[2-amino-3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (4.32 g, 7.70 mmol) and triethylamine (1.17 g, 11.56 mmol) in tetrahydrofuran (73 mL) and stir at room temperature 1 hour. Pour into
5 ethyl acetate and wash with saturated aqueous ammonium chloride and saturated aqueous sodium chloride. Dry (magnesium sulfate), filter and concentrate. Purify on 330 g silica gel eluting with 100:0 to 40:60 hexanes:ethyl acetate to give 0.850 g of the desired compound as an oil.

MS(ES): m/z = 603.5.

10 (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

Stir (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-3-(3-benzyloxy-5-fluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-
15 butyl ester (0.81 g, 1.34 mmol) and 10% palladium on carbon (0.50 g, 1.41 mmol) in ethanol (20 mL) under a hydrogen atmosphere for 3 hours. Filter and concentrate to give 0.652 g (94.7%) of the desired compound as a white solid.

MS(ES): m/z = 511.2.

20 (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester

Add 1-bromo-2-methyl-propane (0.05 g, 0.35 mmol) to (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (0.12 g, 0.23 mmol) and
25 cesium carbonate (0.15 g, 0.46 mmol) in N,N-dimethylformamide (3 mL) under nitrogen and heat in a 60 °C oil bath for 2.5 hours. Cool to room temperature and dilute with ethyl acetate. Wash (0.1N citric acid, 10% potassium carbonate, saturated aqueous sodium chloride), dry (magnesium sulfate), filter and concentrate. Purify on 12 g silica gel column eluting with 100:0 to 40:60 hexanes:ethyl acetate to give 0.072 g (54.5%) of the
30 title compound as a white foam.

The compounds of Preparations 355 – 360 may be prepared essentially as described in Preparation 354.

| Prep. | Compound | MS (ES+) |
|-------|---|-------------------------|
| 355 | (2R,3S,5R)-5-{(1S,2S)-2-Acetylamino-3-[3-(2-ethyl-butoxy)-5-fluoro-phenyl]-1-hydroxy-propyl}-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 597.5 |
| 356 | (2R,3S,5R)-5-{(1S,2S)-2-Acetylamino-3-[3-fluoro-5-(3-methyl-butoxy)-phenyl]-1-hydroxy-propyl}-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 527.2 (loss of t-Bu) |
| 357 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-allyloxy-5-fluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 553.5 |
| 358 | (2R,3S,5R)-5-{(1S,2S)-2-Acetylamino-3-[3-fluoro-5-(3-methyl-but-2-enyloxy)-phenyl]-1-hydroxy-propyl}-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 581.5 |
| 359 | (2R,3S,5R)-5-{(1S,2S)-2-Acetylamino-3-[3-fluoro-5-(2,2,2-trifluoroethoxy)-phenyl]-1-hydroxy-propyl}-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 595.5 |
| 360 | (2R,3S,5R)-5-{(1S,2S)-2-Acetylamino-3-[3-fluoro-5-(2-fluoroethoxy)-phenyl]-1-hydroxy-propyl}-2-(3-fluoro-2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | 635.3 [M+AcO] |

Preparation 361

5

4,4-difluoro-6-methylheptanoic acid

Benzyl 6-methyl-4-oxoheptanoate

Add benzyl chloroformate (0.712 g, 4.17 mmol), triethylamine (0.464 g, 4.59 mmol), and 4-dimethylaminopyridine (0.051 g, 0.42 mmol) to a solution of 6-methyl-4-oxo-heptanoic acid (0.66 g, 4.17 mmol) in dichloromethane (13 mL) at 0°C. Stir at 0°C for 1 hour. Add saturated aqueous ammonium chloride (30 mL). Extract with dichloromethane (1 x 50 mL). Dry organic phase over magnesium sulfate and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with 0-50% ethyl acetate in hexane to provide 0.87 g (84.1%) of the desired compound.

GCMS: $m/z = 248.0$ [M]

15

Benzyl 4,4-difluoro-6-methylheptanoate

Add bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor™, 0.606 g, 2.74 mmol, Aldrich) and ethanol (0.019 mL) to a solution of benzyl 6-methyl-4-oxo-

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heptanoate (0.40 g, 1.61 mmol) in dichloromethane (0.8 mL) in a plastic vessel at 40°C for 4 days. Add Deoxo-fluor™ (1.7 equivalents) and stir 24 hours at 60°C. Add 25 mL aqueous sodium bicarbonate. Extract with dichloromethane (2 x 50 mL). Concentrate the organic phase under reduced pressure and subject the residue to silica gel

5 chromatography, eluting with 0-15% ethyl acetate in hexane to provide the desired compound (0.096 g, 22.0%)

GCMS: $m/z = 270.0$ [M]

Deprotection

10 Add 0.01 g 10% palladium on carbon to a solution of benzyl 4,4-difluoro-6-methyl heptanoate (0.095 g, 0.35 mmol) in 3.5 mL tetrahydrofuran. Hydrogenate under balloon pressure over night. Filter through a pad of celite and wash with pad with ethyl acetate. Concentrate under reduced pressure to provide 0.068 g of the title compound.

MS: $m/z = 179.1$ [M-1]

15

Preparation 362

2-fluoropropionic acid

Heat a solution of ethyl 2-fluoropropionate (0.30 g, 2.50 mmol) in 5M sulfuric acid (5 mL) at 120°C for 1 hour. Saturate the solution with sodium chloride and extract
20 with diethyl ether (4 x 40 mL). Dry the combined organic extracts with magnesium sulfate and concentrate under reduced pressure to provide 0.18 g (78.3%) of the title compound.

GCMS: $m/z = 92.0$ [M]

Preparation 363

25 4,4,4-trifluoro-2-methylbut-2-enoic acid

Heat a solution of ethyl 4,4,4-trifluoro-2-methylbut-2-enoic acid (0.544 g, 2.99 mmol) in 5M sulfuric acid (5 mL) at 120°C for 2.5 days. Saturate the solution with sodium chloride and extract with diethyl ether (1 x 40 mL). Dry the organic phase with magnesium sulfate and concentrate under reduced pressure to provide 0.288 g (62.6%) of
30 the title compound.

MS: $m/z = 153.2$ [M-1]

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Preparation 364

N,N-dipropyl 2-methylsuccinamic acid

Add 40% palladium on carbon (0.064 g) to a solution of (E)-3-dipropylcarbamoyl-2-methylacrylic acid (0.20 g, 0.94 mmol) in tetrahydrofuran (20 mL). Hydrogenate at 60 psi for 18 hours. Filter through a filtering agent and concentrate filtrate under reduced pressure. Subject residue to silica gel chromatography, eluting with dichloromethane containing 10-40% of 5% (2:1 methanol:acetic acid) in dichloromethane to provide the title compound (0.134 g, 66.4%).

MS: $m/z = 216.2$ [M+1]

Preparation 365

cis-2-(methyl-propylcarbamoyl)-cyclopropane carboxylic acid

Add diisopropylethylamine (2.68 mL, 15.4 mmol) and cis-cyclopropane-1,2-dicarboxylic acid (0.50 g, 3.84 mmol) to a slurry of 2-chlorotrityl chloro resin (3.00 g, Nova Bio) in 7:1 dichloromethane:dimethylformamide (10.0 mL). Stir over night and then filter the slurry. Wash the resin with 17:2:1 dichloromethane:methanol:dimethylformamide (3 x 20 mL) followed by dichloromethane (3 x 20 mL). Add the filtered resin to a solution of diisopropylethylamine (1.34 mL, 7.69 mmol), methylpropylamine (0.788 mL, 7.69 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (2.915 g, 7.69 mmol), and HOBt (1.177 g, 7.69 mmol) in dimethylformamide (10 mL) and shake for 2.5 days. Filter and wash the resin with dimethylformamide (3 x 20 mL) and dichloromethane (5 x 20 mL). Add trifluoroacetic acid (1 mL) to a slurry of the washed resin in dichloromethane (20 mL). Shake for 45 minutes and filter. Wash the resin with dichloromethane (2 x 20 mL) and concentrate this filtrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with dichloromethane containing 10-40% of 5% (2:1 methanol:acetic acid) in dichloromethane to provide the title compound (0.247 g, 34.7%).

MS: $m/z = 186.2$ [M+1]

Preparation 366

(+/-)-trans-2-difluoromethyl-cyclopropane carboxylic acid(+/-)-trans-cyclopropane-1,2-dicarboxylic acid monoethyl ester

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Add a solution of 0.709 g (17.72 mmol) sodium hydroxide in 7.38 mL ethanol to a solution of (+/-)-trans-cyclopropane-1,2-dicarboxylic acid diethyl ester (3.00 g, 16.11 mmol) in 36.9 mL acetone. Stir at room temperature for 24 hours. Pour reaction mixture into 100 mL water and extract with ethyl acetate (1 x 70 mL). Acidify the aqueous layer with 5N HCl and concentrate under reduced pressure. Add ethyl acetate and filter the resulting slurry. Concentrate the filtrate under reduced pressure to provide the desired compound (2.26 g, 88.7%).

MS: m/z = 157.2 [M-1]

10 (+/-)-trans-2-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester

Add isobutylchloroformate (0.41 mL, 3.16 mmol) and N-methylmorpholine (0.35 mL, 3.16 mmol) to a solution of (+/-)-trans-cyclopropane-1,2-dicarboxylic acid monoethyl ester (0.50 g, 3.161 mmol) in tetrahydrofuran (21 mL) at -50°C. Stir for 5 minutes and then filter into a slurry of sodium borohydride (0.084 g, 2.21 mmol) in tetrahydrofuran (9 mL) and cool to -50°C. Warm to room temperature over night and then add 9 mL of water. Remove tetrahydrofuran under reduced pressure and extract aqueous layer with diethyl ether (3 x 20 mL). Wash combined organic layers with saturated aqueous sodium chloride and dry over magnesium sulfate. Concentrate under reduced pressure and subject residue to silica gel chromatography eluting with 25-65% ethyl acetate in hexanes to provide the desired compound (0.224 g, 49.1%).

GCMS: m/z = 144.0 [M]

(+/-)-trans-2-formyl-cyclopropanecarboxylic acid ethyl ester

Cool a solution of (+/-)-trans-2-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester (0.22 g, 1.53 mmol) in 1.5 mL DMSO to 0°C. Add to the frozen solution triethylamine (0.85 mL, 0.62 mmol) followed by sulfur trioxide pyridine (0.49 g, 3.05 mmol). Warm reaction mixture to 12°C over 3.5 hours, dilute with diethyl ether (80 mL), and wash with 5% aqueous citric acid (3 x 20 mL) followed by saturated aqueous sodium chloride (1 x 20 mL). Dry over magnesium sulfate and concentrate under reduced pressure to provide the desired compound.

GCMS: m/z = 142 [M]

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(+/-)-trans-2-difluoromethyl-cyclopropanecarboxylic acid ethyl ester

Add a solution of Deoxo-fluorTM (0.32 mL, 1.73 mmol) in 0.3 mL dichloromethane to a solution of (+/-)-trans-2-formyl-cyclopropanecarboxylic acid ethyl ester (0.145 g, 1.02 mmol) in 0.5 mL dichloromethane. Stir the reaction mixture for 16 hours, pour into saturated aqueous sodium bicarbonate (15 mL), and extract with dichloromethane (3 x 20 mL). Dry the combined organic extracts over sodium sulfate, concentrate under reduced pressure, and subject residue to silica gel chromatography, eluting with 25-65% ethyl acetate in hexanes to provide the desired compound (0.087 g, 52.2%).

Ester hydrolysis

Add 1.32 mL 2M LiOH to a solution of (+/-)-trans-2-difluoromethyl-cyclopropanecarboxylic acid ethyl ester (0.087 g, 0.53 mmol) in tetrahydrofuran (13.3 mL). Stir for 4 hours and then concentrate under reduced pressure to a volume of about 1.5 mL. Dilute with water (10 mL) and extract with diethyl ether (1 x 25 mL). Acidify the aqueous layer with 1.0 N HCl and extract with diethyl ether (5 x 25 mL). Dry combined organic layers over magnesium sulfate and concentrate under reduced pressure to provide the title compound as a yellow oil (0.057 g, 79.6%)

MS: $m/z = 135.2$ [M-1]

Preparation 367

(+/-)-trans-2-fluoromethyl-cyclopropane carboxylic acid

The title compound is prepared by reacting (+/-)-trans-2-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester with Deoxo-fluorTM followed by ester hydrolysis essentially as described in Preparation 366.

GCMS: $m/z = 118.0$ [M]

Preparation 368

3-butyl-5-fluorobenzaldehyde

3-bromo-5-fluorobenzaldehyde

Add dropwise a solution of 1,3-dibromo-5-fluorobenzene (12.39 mL, 98.5 mmol) in tetrahydrofuran (20 mL) to a solution of n-butyllithium (64.61 mL, 103.4 mmol, 1.6 M

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in hexanes) in tetrahydrofuran (55 mL) at -78°C. Stir at -78°C for 45 minutes, add dimethylformamide (7.62 mL, 98.5 mmol), stir at -78°C for 1.5 hours, remove cooling bath and stir 10 minutes. Add saturated aqueous ammonium chloride (150 mL) and extract with diethyl ether (2 x 700 mL). Wash combined organic layers sequentially with water (1 x 300 mL) and saturated aqueous sodium chloride (1 x 300 mL). Dry over magnesium sulfate and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with 0-10% ethyl acetate in hexanes to provide the desired compound (11.05 g, 55.3%).

GCMS: m/z = 203.0 [M]

3-butyl-5-fluorobenzaldehyde

Add butylzinc bromide (49.3 mL, 24.6 mmol, 0.5 M in THF) followed by Pd(dppf)₂Cl₂ dichloromethane complex (1.01 g, 1.23 mmol) to a solution of 3-bromo-5-fluorobenzaldehyde (5.00 g, 24.6 mmol) in tetrahydrofuran (123.1 mL). Stir at room temperature in a sealed vessel flushed with nitrogen for 18 hours. Add saturated aqueous ammonium chloride (125 mL). Separate the layers and extract the aqueous layer with ethyl acetate (1 x 300 mL). Wash combined organic layers with saturated aqueous sodium chloride, dry over magnesium sulfate and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with 0-10% ethyl acetate in hexanes to provide the title compound (3.43 g, 77.3%).

GCMS: m/z = 180.0 [M]

Beginning with nitromethane and appropriately substituted benzaldehydes and formylmorpholines, the following compounds may be prepared essentially as described in Preparation 188.

| Prep | Compound | MS (ES) [M+Na] |
|------|---|-------------------|
| 369 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(4-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 519.3 |
| 370 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-(trifluoromethylthio)phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 601.3 |
| 371 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic | 519.2 |

| | | |
|-----|---|-------|
| | acid <i>tert</i> -butyl ester | |
| 372 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(2,4-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 537.3 |
| 373 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-(trifluoromethyl)phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 569.3 |

Preparation 374

(1S,2S)-2-Amino-3-(3,5-difluorobenzyl)-1-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol

5 Dibenzyl-[(1S,2S)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-ethyl]-amine

React 2,2-di-(fluoromethyl)propanol (2.172 g, 17.5 mmol) with (3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-ol (2.004 g, 3.5 mmol) essentially as described in Preparation 307 to provide 1.0 g
10 of the desired compound.

Deprotection

Charge a deoxygenated solution of dibenzyl-[(1S,2S)-2-benzyloxy-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-ethyl]-amine (0.95 g, 1.399 mmol) in *tert*-butanol (17.48 mL) with 20% palladium(II)
15 hydroxide on carbon (2.137 g, 3.06 mmol) and hydrogenate at 60 psi for 4 hours. Dilute reaction mixture with ethyl acetate and filter through Celite™. Concentrate filtrate to provide the title compound (0.571 g).

20

Preparation 378

(1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,6R)-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-propan-1-ol

(2R,5R)-5-[(1S,2S)-2-Dibenzylamino-3-[3,5-difluorophenyl]-1-benzyloxy-propyl]-2-(2,2-di-(fluoromethyl)-propoxy)-morpholine-4-carboxylic acid *tert*-butyl ester

25 React (3S,5R)-5-[(1S,2S)-2-Dibenzylamino-3-[3,5-difluorophenyl]-1-benzyloxy-propyl]-2-hydroxymorpholine-4-carboxylic acid *tert*-butyl ester (1.0 g, 1.52 mmol) with trifluoromethanesulfonic acid 2,2-di-(fluoromethyl)propyl ester (584 mg, 2.27 mmol)

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essentially as described in Preparation 306 to provide 1.0 g (86%) of the desired compound.

5 (2R,3S,5R)-5-{(1S,2S)-2-Amino-3-[3,5-difluorophenyl]-1-hydroxy-propyl}-2-(2,2-di-
(fluoromethyl)-propoxy)-morpholine-4-carboxylic acid tert-butyl ester

Charge a deoxygenated solution of (2R,3S,5R)-5-{(1S,2S)-2-dibenzylamino-3-[3,5-difluorophenyl]-1-benzyloxy-propyl}-2-(2,2-di-(fluoromethyl)-propoxy)-morpholine-4-carboxylic acid tert-butyl ester (1.0 g, 1.3 mmol) in 16.99 mL ethyl acetate with 20% palladium(II) hydroxide (1.0 g, 1.40 mmol) and hydrogenate at atmospheric
10 pressure over night. Filter the reaction mixture through Celite™ and concentrate the filtrate under reduced pressure to provide 0.629g (98%) of the desired compound in crude form.

N-Deprotection

15 Add cold (0°C) trifluoroacetic acid to (2R,3S,5R)-5-{(1S,2S)-2-amino-3-[3,5-difluorophenyl]-1-hydroxy-propyl}-2-(2,2-di-(fluoromethyl)-propoxy)-morpholine-4-carboxylic acid tert-butyl ester (364 mg, 0.73 mmol) and stir the solution at 0°C for 10 minutes. Allow reaction mixture to warm to room temperature over 20 minutes and concentrate under reduced pressure. Dissolve resultant oil in ethyl acetate and add
20 saturated aqueous sodium bicarbonate. Wash the organic layer with saturated aqueous sodium bicarbonate, dry over sodium sulfate, and concentrate to provide the title compound.

Preparation 378

25 (1S,2S)-2-Amino-3-(3-isopropylsulfanyl-5-fluorophenyl)-1-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol

Heat a mixture of (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol (91 mg, 0.22 mol) and sodium 2-propanethiolate (328 mg, 3.34 mmol) in N-methylpyrrolidin-2-one (2.0 mL) at
30 90°C in a sealed tube for 1 hour. Cool the reaction mixture to room temperature, dilute with methanol, add ammonium chloride (192 mg, 3.34 mmol), and mix well. Load

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mixture on SCXTM column and elute with 2.0 M ammonia in methanol to provide the desired compound (60 mg, 58%).

MS(ES): $m/z = 465$ [$M^+ + H$]

The compounds of Preparations 379 – 381 may be prepared essentially as described in Preparation 378.

| Prep | Compound | MS(ES) |
|------|--|----------------------|
| 379 | (1S,2S)-2-Amino-3-(3-propylsulfanyl-5-fluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 451 [$M^+ + H$] |
| 380 | (1S,2S)-2-Amino-3-(3-(2-methylprop-2-yl)sulfanyl-5-fluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 479 [$M^+ + H$] |
| 381 | (1S,2S)-2-Amino-3-(3-phenylsulfanyl-5-fluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 499 [$M^+ + H$] |

Preparation 382

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester
(2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester

Beginning with (3S,5R)-5-[(1S,2S)-1-Benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-ol, the desired compound may be prepared essentially as described in Preparation 307.

(2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester

Stir a mixture of sodium hydride (115 mg, 2.89 mmol, 60% in mineral oil) in N-methyl-2-pyrrolidinone (960 μ L) and 1-propanol (234 μ L) for 10 minutes and then add a solution of (2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester (440 mg, 0.57 mmol) in N-methyl-2-pyrrolidinone (1 mL) and stir in a sealed vial at 90°C for 4 hours. Cool to room temperature and pour reaction mixture into water and extract well with ethyl acetate. Wash the organic phase with water followed by

saturated aqueous sodium chloride and concentrate under reduced pressure. Subject the resulting residue to silica gel chromatography, eluting with hexane containing from 0 - 50% ethyl acetate to provide the desired compound.

5 Deprotection

Beginning with (2R,3S,5R)-5-[(1S,2S)-1-Benzoyloxy-2-dibenzylamino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester (350 mg, 0.436 mmol), the title compound may be prepared essentially as described in Preparation 307.

10

The compounds of Preparations 383 - 384 may be prepared essentially as described in Preparation 382.

| Prep | Compound | MS(ES) |
|------|---|----------------------------|
| 383 | (1S,2S)-2-Amino-3-(3-propoxy-5-fluorophenyl)-1-[(3R,5S,6R)-6-(2,2,2-tri-(fluoromethyl)ethoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 467 [M ⁺ +H] |
| 384 | (1S,2S)-2-Amino-3-(3-propoxy-5-fluorophenyl)-1-[(3R,5S,6R)-6-(trimethylsilylmethoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 429 [M ⁺ +H] |

Employing the appropriate alcohol in place of 1-propanol, the compounds of

15 Preparations 385-393 may be prepared essentially as described in Preparation 382.

| Prep | Compound | MS(ES) |
|------|---|------------------------------|
| 385 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-hydroxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 489.3 [M ⁺ +H] |
| 386* | (1S,2S)-2-Amino-3-(3-cyclopropylmethoxy-5-fluoro-phenyl)-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-propan-1-ol | 461 [M ⁺ +H] |
| 387* | (1S,2S)-2-Amino-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-3-(3-fluoro-5-isobutoxy-phenyl)-propan-1-ol | 463 [M+H] ⁺ |
| 388* | (1S,2S)-2-Amino-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-3-[3-fluoro-5-(2-methyl-cyclopropylmethoxy)-phenyl]-propan-1-ol | 475 [M+H] ⁺ |
| 389* | (1S,2S)-2-Amino-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-3-[3-fluoro-5-(1-methyl-cyclopropylmethoxy)-phenyl]-propan-1-ol | 475 [M+H] ⁺ |
| 390* | (1S,2S)-2-Amino-3-[3-(1-cyclopropyl-ethoxy)-5-fluoro-phenyl]-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-propan-1-ol | 475 [M+H] ⁺ |

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| | | |
|------|--|----------------------------|
| 391 | 5-[2-amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-3-methyl-morpholine-4-carboxylic acid <i>tert</i> -butyl ester | |
| 392* | 2-amino-3-[3-(2,2-dimethyl-propoxy)-5-fluoro-phenyl]-1-[6-(3-fluoro-2,2-bis-(fluoromethyl)-ethoxy)-5-methyl-morpholin-3-yl]-propan-1-ol | 495 [M+H ⁺] |
| 393* | 3-[(2S,3S)-2-Amino-3-[(3R,5S,6R)-(6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl)-3-hydroxy-propyl]-5-fluoro-phenol | 407 |

*Hydrogenated under conditions of Preparation 374.

Preparation 394

(1S,2S)-2-Amino-3-(3-(2,2-dimethylpropoxy)-5-fluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol

- 5 Beginning with (1S,2S)-2-Amino-3-(3,5-difluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol (196 mg, 0.48 mmol) and neopentyl alcohol (465 mg, 5.28 mmol), the title compound may be prepared essentially as described in Preparation 382.

- 10 Compounds of Preparations 395 – 397 may be prepared essentially as described in Preparation 394.

| Prep | Compound | MS(ES) |
|------|---|------------------------------|
| 395 | (1S,2S)-2-Amino-3-(3-cyclopropylmethoxy-5-fluorophenyl)-1-(3R,5S,6R)-6-(3-fluoro-2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol | |
| 396 | (1S,2S)-2-Amino-3-(3-cyclobutoxy-5-fluorophenyl)-1-(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol | |
| 397 | (1S,2S)-2-Amino-3-(3-isobutoxy-5-fluorophenyl)-1-(3R,5S,6R)-6-(3-fluoro-2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol | 445.3 [M ⁺ +H] |

Preparation 398

- (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetyl-amino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester
- 15 Add acetic anhydride (43 μ L, 0.44 mmol) to a solution of (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester (231 mg, 0.44 mmol) and triethylamine (92 μ L, 0.65 mmol) in dichloromethane (4.6 mL) and stir at room
- 20 temperature for 30 minutes. Concentrate reaction mixture under a stream of nitrogen and

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subject residue to silica gel chromatography, eluting with 0-100% ethyl acetate in hexane to provide the title compound.

Compounds of Preparations 399 – 405 may be prepared essentially as described in Preparation 398.

| Prep | Compound | MS(ES) |
|------|---|---|
| 399 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-hydroxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 400 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3,5-difluorophenyl)-propyl]-2-(2-methoxypropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 539.0 [M ⁺ +Na ⁺] |
| 401 | 2R,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(cyclopropylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 525.3 [M ⁺] |
| *402 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-bromo-5-fluoro-phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 577.4 [M ⁺ +H] |
| *403 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-butyl-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553.5 [M ⁺ +H] |
| *404 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(4-methyl-3,5-difluoro-phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 529.5 [M ⁺ +H] |
| *405 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(4-(3-methylbutyl)-3,5-difluoro-phenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 607.3 [M ⁺ +H] |

5 *Replace dichloromethane with tetrahydrofuran as reaction solvent.

Beginning with (2RS,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-methylmorpholin-2-ol, the following compounds may be prepared essentially as described in Preparation 307.

| Prep | Compound | MS(ES) |
|------|--|------------------------------|
| 406 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3,5-difluorophenyl)-propyl]-2-(2-methoxypropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 407 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <u>tert</u> -butyl ester | 473.4 [M ⁺ +H] |

10

Preparation 408

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-bromo-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

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3-Butyl-5-fluoro-benzaldehyde

Dissolve 1,3-Dibromo-5-fluoro-benzene (12.00 g, 0.05 mmol) in diethyl ether (470 mL) and cool to -78 C. Slowly add 1.6 M n-butyllithium in hexanes (29.5 mL, 49.6 mmol) and stir at -78 for one hour. Add dimethylformamide (3.45 g, 0.05 mmol) dropwise and warm to room temperature overnight. Quench with saturated aqueous ammonium chloride solution. Separate the layers and extract the organic layer (1 x 300 mL) with diethyl ether. Combine the organic layers and wash (1 x 150 mL) with water, (1 x 100 mL) with saturated aqueous sodium chloride and dry over magnesium sulfate. Purify using medium pressure chromatography (silica gel, 0-10% diethyl ether:hexanes) to give the desired product (4.15 g, 43%) as a yellow liquid.

2-(3-bromo-5-fluorophenyl)-1-nitroethane

Beginning with 3-bromo-5-fluorobenzaldehyde, the desired compound may be prepared essentially as described in Preparation 168.

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-bromo-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Beginning with 2-(3-bromo-5-fluorophenyl)-1-nitroethane, the desired compound may be prepared essentially as described in Preparation 188.

Reduction

Add zinc (0.604 g, 9.23 mmol) to a solution of (2R,3S,5R)-5-[(1R,2S)-3-(3-bromo-5-fluoro-phenyl)-1-hydroxy-2-nitro-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (0.520 g, 0.923 mmol) in acetic acid (9.23 mL). Stir the reaction mixture for 22 hours at room temperature. Filter the reaction mixture and wash the filter cake with cold water (100 mL). Add saturated aqueous sodium bicarbonate to the filtrate to neutralize the acid. Extract the neutralized aqueous phase with ethyl acetate (3 x 250 mL). Dry the combined organic phases with magnesium sulfate and concentrate under reduced pressure to provide the title compound (0.49 g, 99.5%) as a white foam.

MS(ES): $m/z = 535.3$ $[M+H]^+$

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Preparation 409

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-propyl-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

- 5 Add propyl zinc bromide (2.311 g) in tetrahydrofuran and (1,1'-bis(diphenylphosphino)ferrocene) palladium(II) chloride (0.015 g) to a solution of (2R,3S,5R)-5-[(1S,2S)-1-hydroxy-2-acetylamino-3-(3-bromo-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.07 g, 0.122 mmol) in tetrahydrofuran (1.2 mL) in a sealed tube flushed with nitrogen. Heat the tube at 65°C for
- 10 6.5 hours. Add saturated aqueous ammonium chloride (5 mL). Extract the reaction mixture with ethyl acetate (2 x 30 mL). Combine the organic phases and wash with saturated aqueous sodium chloride (1 x 15 mL), dry over magnesium sulfate and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with hexanes containing 15-45% ethyl acetate, to provide 0.039 g (60%) of the title
- 15 compound as an off-white foam.

MS(ES): $m/z = 539.5$ $[M+1]^+$

Preparation 410

- (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-fluoro-5-(3-methyl-butyl)-phenyl]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester
- 20

- Beginning with 3-methylbutyl zinc bromide and (2R,3S,5R)-5-[(1S,2S)-1-hydroxy-2-acetylamino-3-(3-bromo-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.165 g, 0.287 mmol), the title
- 25 compound (0.127 g, 78%) may be prepared essentially as described in Preparation 409.
- MS(ES): $m/z = 565.3$ $[M-1]^-$

Preparation 411

- (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-(2-ethoxyphenyl)-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester
- 30

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Add 2-ethoxyphenylboronic acid (0.065 g, 0.394 mmol) and (1,1'-bis(diphenylphosphino)ferrocene) palladium(II) chloride (0.021 g) to a mixture of 2M sodium carbonate solution (0.262 g, 0.525 mmol) and (2R,3S,5R)-5-[(1S,2S)-1-hydroxy-2-acetylamino-3-(3-bromo-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.151 g, 0.262 mmol) in tetrahydrofuran (2.62 mL) in a sealed tube flushed with nitrogen. Heat the tube at 80°C for 3 days. Add saturated aqueous sodium chloride and extract with ethyl acetate (2 x 50 mL). Dry over magnesium sulfate and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with hexanes containing 25-50% ethyl acetate to provide the title compound (0.075 g, 46%) as a white foam.

MS(ES): $m/z = 639.3$ $[M+23]^+$

Preparation 412

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(4-methyl-3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

(2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(4-methyl-3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester

Add n-butyllithium (252 μ L, 0.404 mmol, 1.6 M in hexanes) dropwise over 5 minutes to a solution of (2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid tert-butyl ester (0.30 g, 0.404 mmol) in tetrahydrofuran (0.6 mL) at -78°C. Add potassium tert-butoxide (0.404 mL, 1 M in tetrahydrofuran) dropwise over 10 minutes and stir the reaction mixture for an additional 10 minutes. Add iodomethane (25.1 μ L, 0.404 mmol) followed by a solution of hexamethylphosphorus triamide (53.7 μ L, 0.294 mmol) in tetrahydrofuran (40.4 μ L). Stir reaction mixture at -78°C for 1 hour. Remove cooling bath and stir for 20 minutes. Add water (20 mL) and extract with ethyl acetate (2 x 50 mL). Wash combined organic layers with water (3 x 20 mL), dry over magnesium sulfate, and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with hexanes containing 0-10% diethyl ether, to provide the desired compound 0.169 g (55.3%) as a white foam.

MS(ES): $m/z = 757.3$ $[M+1]^+$.

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Hydrogenation

Add 20% palladium on carbon (0.085 g) to a solution of (2R,3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(4-methyl-3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester (0.169 g, 0.223 mmol) in ethyl acetate (3.00 mL) and hydrogenate at balloon pressure for 16 hours. Add additional 20% palladium on carbon (170 mg) and continue hydrogenation for 8 hours. Filter reaction mixture over a pad of filtering agent and wash pad with ethyl acetate. Concentrate filtrate to provide the title compound (0.109 g) as an off-white foam.

MS(ES): $m/z = 487.3 [M+1]^+$

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Preparation 413

(2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(4-(3-methylbutyl)-3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester

Using 3-methylbutyl iodide, the title compound may be prepared essentially as described in Preparation 412.

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MS(ES): $m/z = 543.3 [M+1]^+$

Replacing dichloromethane with tetrahydrofuran, the compounds of Preparations 414 – 416 may be prepared essentially as described in Preparation 219.

| Prep | Compound | MS(ES) |
|------|--|------------------------------|
| 414 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-(6-methylheptanoylamino)-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 585.5 [M ⁺ +H] |
| 415 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-(6-methyl-4,4-difluoroheptanoylamino)-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 635.5 [M ⁺ +H] |
| 416 | (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-(6-methyl-4,4-difluoroheptanoylamino)-3-(3-butyl-5-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid <i>tert</i> -butyl ester | 673.6 [M ⁺ +H] |

20

Preparation 417

(2R,5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(cyclopropylmethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester

Beginning with (3S,5R)-5-[(1S,2S)-1-Benzyloxy-2-dibenzylamino-3-(3-benzyloxy-5-fluorophenyl)-propyl]-3-methylmorpholin-2-one, the desired compound may be prepared essentially as described in Preparation 306.

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MS(ES): $m/z = 483.3 [M^+]$

Preparation 418

(2R,3S5R)-5-[(1S,2S)-1-Hydroxy-2-amino-3-(3-trifluoromethoxyphenyl)-propyl]-2-(2,2-di(fluoromethyl)propoxy)-3-methylmorpholine
(R)-4-[(1R,2S)-1-Hydroxy-2-nitro-3-(3-trifluoromethoxy-phenyl)-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

Beginning with 2-(3-trifluoromethoxyphenyl)-1-nitroethane the desired compound may be prepared essentially as described in Preparation 168.

MS(ES): $m/z = 463.3 [M^+]$

(R)-4-[(1S,2S)-2-Amino-1-hydroxy-3-(3-trifluoromethoxy-phenyl)-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

Add zinc (8.46 g, 129.4 mmoles) to (R)-4-[(1R,2S)-1-Hydroxy-2-nitro-3-(3-trifluoromethoxy-phenyl)-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (6.01 g, 12.9 mmoles) in acetic acid (75 mL) and stir at room temperature for 10 minutes. Filter and wash the solids with water. Extract with ethyl acetate. Wash organic layer with 0.1 N sodium hydroxide and saturated aqueous sodium chloride. Dry over sodium sulfate, filter and concentrate to give 5.18 g (92% yield) of the title compound as a white solid.

MS (ES+): $m/z = 435.0 [M^+]$

(2R,3R,4S)-2-Amino-3-benzyloxy-4-dibenzylamino-5-(3-trifluoromethoxy-phenyl)-pentan-1-ol

Beginning with (R)-4-[(1S,2S)-2-Amino-1-hydroxy-3-(3-trifluoromethoxy-phenyl)-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester, the desired compound may be prepared essentially as described in Preparation 167.

MS (ES+): $m/z = 565.3 [M^+]$

Beginning with (2R,3R,4S)-2-Amino-3-benzyloxy-4-dibenzylamino-5-(3-trifluoromethoxy-phenyl)-pentan-1-ol, the title compound may be prepared essentially as described in Preparation 307 with the exception of protecting the morpholine nitrogen

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with tert-butoxycarbonyl and replacing 20% palladium hydroxide with 10% palladium hydroxide in the hydrogenolysis step.

MS (ES+): $m/z = 457.3$ [M^+]

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Preparation 419

(3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3-benzyloxy-5-fluorophenyl)-propyl]-morpholin-2-one-4-carboxylic acid tert-butyl ester
(R)-4-[(1R,2S)-3-(3-benzyloxy-5-fluorophenyl)-1-benzyloxy-2-dibenzylaminopropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

10

Add NaH (12.5 g, 60% mineral oil suspension, 312.5 mmol) in portions to a solution of benzyl alcohol (32 mL, 309.2 mmol) in N-methylpyrrolidinone (1 L). Stir the reaction mixture at r.t. until no gas evolution is detected. Add (R)-4-[(1R,2S)-3-(3,5-difluorophenyl)-1-benzyloxy-2-dibenzylaminopropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (130 g) to the mixture and warm it up to 90°C. After 45

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min, allow to cool to room temperature and add saturated aqueous ammonium chloride. Dilute with ethyl acetate (2 L) and wash with saturated aqueous sodium chloride (2 x 1.5 L). Dry the organic layer on MgSO₄, filter and concentrate. Subject residue to silical gel chromatography, eluting with 2-4% ethyl acetate in hexanes, to provide 139.45 g (94%) of the desired compound as a white solid.

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LCMS: $m/z = 745$ (M+1)

(2R,3S,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3-benzyloxy-2-fluorophenyl)-pentan-1-ol

25

Add concentrated hydrochloric acid (22.7 mL) to a solution of (R)-4-[(1R,2S)-3-(3-benzyloxy-5-fluorophenyl)-1-benzyloxy-2-dibenzylaminopropyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (25.89 mmol, 19.3g) in 88 mL methyl tert-butyl ether. Stir at room temperature for 3 hours. Add additional concentrated hydrochloric acid (10 mL) and stir for 1 hour. Add dichloromethane (300mL) and adjust to pH 12 with NaOH. Separate the two phases and dry the organic phase over magnesium sulfate.

30

Concentrate under reduced pressure and subject the residue to silica gel chromatography, eluting with dichloromethane containing 0-5% 3 M ammonia in methanol, to provide 15 g (96%) of the desired compound.

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(3S)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3-benzyloxy-5-fluorophenyl)-propyl]-morpholin-2-one

Add phenyl bromoacetate (4.94g, 23mmol) to a solution of (2R,3S,4S)-2-amino-3-benzyloxy-4-dibenzylamino-5-(3-benzyloxy-2-fluorophenyl)-pentan-1-ol (12.7g, 21 mmol) and diisopropylethylamine (11 mL, 63 mmol) in dimethylformamide (210 mL). Stir at room temperature for 20 hours. Dilute the reaction mixture with ethyl acetate and saturated aqueous sodium chloride. Extract the aqueous phase well with ethyl acetate. Wash the combined organic phases well with saturated aqueous sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with hexane containin 0-40% ethyl acetate to provide 12 g (89%) of the desired compound.

Morpholine nitrogen protection

Add BOC₂O (6.9 g, 31.64 mmol) to a solution of the morpholin-2-one (12g, 18.6 mmol) in dichloromethane (180 mL) and diisopropylethylamine (8.1 mL, 46.5 mmol). Stir at room temperature for 6 hours. Add dichloromethane and wash with 5% citric acid solution. Wash the organic phase with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. Dry over magnesium sulfate and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with 9:1 hexane:methyl tert-butyl ether to provide 10.4g (75%) of the title compound.

Preparation 420

(1S,2S)-2-Amino-3-(3-cyclopropylmethoxy-phenyl)-1-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-propan-1-ol trifluoroacetate
(2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-hydroxy-phenyl)-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid benzyl ester trifluoroacetate

Add trifluoroacetic acid (3 mL) to (2R,3S,5R)-5-[(1S,2S)-2-acetylamino-1-hydroxy-3-(3-hydroxy-phenyl)-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (84 mg, 0.17 mmol). Stir 40 minutes and evaporate to give N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-1-(3-hydroxy-benzyl)-ethyl]-acetamide trifluoroacetate (115 mg). Add

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diisopropylethyl-amine (0.074 mL, 0.425 mmol) dropwise to an ice cold solution of N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-1-(3-hydroxy-benzyl)-ethyl]-acetamide (115 mg) and benzyl chloroformate (0.029 mL, 0.20 mmol) in tetrahydrofuran (4 mL). Stir 30 minutes and add an additional portion of diisopropylethylamine (0.074 mL) and benzyl chloroformate (0.025 mL). Stir 50 minutes and warm to ambient temperature, stir 10 minutes and dilute with saturated aqueous sodium chloride followed by ethyl acetate and 1N aqueous hydrochloric acid. Separate layers and wash organic phase with saturated aqueous sodium chloride, dry with magnesium sulfate. Purify on silica gel with dichloromethane/ethyl acetate mixtures to give the desired compound (69 mg) as a white foam. MS(ESI): $m/z = 529$ $[M+H]^+$.

N-{(S)-2-(3-Cyclopropylmethoxy-phenyl)-1-[(1S,5S,6R,8aR)-6-(2,2-dimethyl-propoxy)-5-methyl-3-oxo-tetrahydro-oxazolo[4,3-c][1,4]oxazin-1-yl]-ethyl}-acetamide

Heat a mixture of (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-hydroxy-phenyl)-propyl]-2-(2,2-dimethyl-propoxy)-3-methyl-morpholine-4-carboxylic acid benzyl ester (69 mg, 0.13 mmol), cyclopropylmethyl bromide (0.019 mL, 0.195 mmol), cesium carbonate (127 mg, 0.39 mmol) and N,N-dimethylformamide (2 mL) to 60°C for 18 hours. Cool and dilute with ethyl acetate and wash with saturated sodium chloride, dry with magnesium sulfate and purify on silica gel with dichloromethane/ethyl acetate mixtures to give the desired compound (53 mg). MS(ESI): $m/z = 475$ $[M+H]^+$.

Deprotection

Heat a solution of N-{(S)-2-(3-cyclopropylmethoxy-phenyl)-1-[(1S,5S,6R,8aR)-6-(2,2-dimethyl-propoxy)-5-methyl-3-oxo-tetrahydro-oxazolo[4,3-c][1,4]oxazin-1-yl]-ethyl}-acetamide (50 mg, 0.107 mmol) in 1:4:4 tetrahydrofuran/methanol/4N sodium hydroxide (2 mL) to 100°C for 18 hours, then cool to ambient temperature. Partition with water and ethyl acetate, wash organic layer with saturated sodium bicarbonate, saturated sodium chloride, dry with magnesium chloride and purify on C-18 reversed phase silica gel to provide the title compound (9 mg). MS(ESI): $m/z = 407$ $[M+H]^+$.

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(2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester
(2S,3S,5R)-5-[(1S,2S)-1-Benzyl-3-(3-benzyl-5-fluoro-phenyl)-2-dibenzylamino-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester

- 5 Add diisopropyl azodicarboxylate (0.675 mL, 3.43 mmol) dropwise to an ice cold solution of (3S,5R)-5-[(1R,2S)-1-benzyl-3-(3-benzyl-5-fluoro-phenyl)-2-dibenzylamino-propyl]-3-methyl-morpholin-2-ol (1.30 g, 1.71 mmol), 2,2,2-trifluoro-ethanol (1.0 mL, 13.7 mmol) and triphenylphosphine (900 mg, 3.43 mmol) in deoxygenated toluene (8 mL). Stir in ice bath for 3 hours and evaporate. Purify on silica
10 gel with hexane/ethyl acetate mixtures to give the desired compound (1.21 g) as a white foam. MS(ESI): $m/z = 843$ $[M+H]^+$.

(2S,3S,5R)-5-[(1S,2S)-2-Amino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester

- 15 Add 20% palladium hydroxide on carbon (200 mg) to a solution of (2S,3S,5R)-5-[(1S,2S)-1-benzyl-3-(3-benzyl-5-fluoro-phenyl)-2-dibenzylamino-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester (116 mg, 0.138 mmol) in *tert*-butanol (10 mL). Heat to 45°C and hydrogenate at 50 psi hydrogen gas for 18 hours. Filter and evaporate to give the desired compound (77 mg). MS(ESI):
20 $m/z = 483$ $[M+H]^+$.

(2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester

- Add acetic anhydride (0.142 mL, 1.51 mmol) to an ice cold solution of
25 (2S,3S,5R)-5-[(1S,2S)-2-Amino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester (823 mg, 1.43 mmol) in dichloromethane (9 mL). Stir for 50 minutes and add diisopropylethylamine (0.125 mL, 0.717 mmol) and stir for 2 hours. Quench with aqueous 1N hydrochloric acid, wash with saturated aqueous sodium bicarbonate, dry with magnesium
30 sulfate and purify on silica gel with dichloromethane/ethyl acetate mixtures to give the desired compound (493 mg). MS(ESI): $m/z = 525$ $[M+H]^+$.

Ether Formation

Heat a mixture of (2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester (169 mg, 322 μ mol), 1-bromopropane (0.044 mL, 0.48 μ mol) and cesium carbonate (315 mg, 0.966 μ mol) in N,N-dimethylformamide (2 mL) to 60°C for 5 hours then cool to ambient temperature. Dilute with ethyl acetate and wash with saturated sodium chloride, dry with magnesium sulfate and purify on silica gel with dichloromethane/ethyl acetate mixtures to give the title compound (153 mg). MS(ESI): $m/z = 567$ [M+H]⁺.

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The compounds of Preparations 422 – 423 may be prepared essentially as described in Preparation 421.

| Prep | Compound | MS(ES) |
|------|---|---------------------------|
| 422 | (2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 581 [M+H] ⁺ |
| 423 | (2S,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2,2-difluoro-ethoxy)-5-fluoro-phenyl]-1-hydroxy-propyl]-3-methyl-2-(2,2,2-trifluoro-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester | 589 [M+H] ⁺ |

Preparation 424

(2R,3S,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-2-((E)-2,5-dimethyl-hex-2-enoylamino)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester

Suspend sodium hydride (60% dispersion) (0.78 g, 19.61 mmol) in tetrahydrofuran (22 mL) and add diethyl phosphite (0.80 g, 6.54 mmol). Add 2-bromopropionic acid (1.00 g, 6.54 mmol) slowly and wait for gas evolution to cease then add 3-methyl-butiraldehyde (0.56 g, 6.54 mmol) and stir at ambient temperature overnight. Quench with ethanol and pour into water. Acidify with 1M HCl and extract with ethyl acetate. Wash with saturated sodium chloride solution, dry over magnesium sulfate and concentrate under reduced pressure. Combine the crude acid (0.01 g, 0.09 mmol) with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.02 g, 0.09 mmol) and 1-hydroxybenzotriazole (HOBt) (0.01 g, 0.09 mmol) in methylene chloride (1 mL) and stir at room temp. under nitrogen for 30 minutes. Add (2R,3S,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluoro-phenyl)-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-

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- 4-carboxylic acid tert-butyl ester (0.04 g, 0.09 mmol) and N,N-diisopropylamine (0.02 g, 0.17 mmol) and continue stirring until starting material is consumed. Dilute with ethyl acetate, wash with saturated potassium carbonate solution and sat'd sodium chloride solution, dry over magnesium sulfate and concentrate in vacuo. Purify by silica gel chromatography eluting with 0% to 10% to 30% ethyl acetate/hexanes. 0.044 g, 66.9 % yield. MS (ES): m/z = 583.3 [M+H]

Preparation 425

- (2R,5R)-5-[(1S,2S)-3-(3,5-Difluoro-phenyl)-1-hydroxy-2-((E)-6,6,6-trifluoro-2-methyl-hex-2-enoylamino)-propyl]-2-(2,2-dimethyl-propoxy)-morpholine-4-carboxylic acid tert-butyl ester

Using 4,4,4-trifluorobutyraldehyde, the title compound may be prepared essentially as described in Preparation 424.

MS (ES): m/z = 621.3 [M-H]

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Preparation 426

1,1-Dimethoxy-pentan-2-one

2-Ethyl-4,4-dimethoxy-3-oxo-butyric acid methyl ester

- Dissolve methyl dimethoxyacetate (11.56 g, 86.16 mmol) in toluene (783 mL) then add sodium hydride (6.90 g, 172.33 mmol) and warm to 70-80 °C. Add methyl butyrate (8.00 g, 78.33 mmol) dropwise and continue heating to 90 degrees. Cool to ambient temperature and dump into 0.5 M HCl. Wash with ethyl acetate (3x) then wash organics with saturated sodium chloride solution, dry over magnesium sulfate and concentrate in vacuo. Purify by distillation. Product boils at 185 °C. 11.5 g, 72% yield.
- ¹H NMR (CDCl₃) δ 0.90 (3H, t), 1.82-1.86 (2 H, m), 3.37 (6H, s), 3.66 (1H, t), 3.68 (3H, s), 4.58 (1H, s).

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Decarboxylation

- Dissolve 2-Ethyl-4,4-dimethoxy-3-oxo-butyric acid methyl ester (5.00 g, 24.49 mmol) in methanol (8 mL) and add potassium hydroxide solution (31.83 mmol) then heat at reflux for 1 hr. Cool to ambient temperature and pour into 40 mL water. Wash with

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diethyl ether, separate organics, dry over magnesium sulfate and concentrate under a stream of nitrogen. 2.5 g, 68% yield.

^1H NMR (CDCl_3) δ 0.91 (3H, t), 1.57-1.63 (2 H, m), 2.52 (2H, t), 3.40 (6H, s), 4.44 (1H, s).

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Preparation 427

3-Fluoro-2,2-dimethyl-propan-1-ol

Add a solution of 3-fluoro-2,2-dimethyl-propionyl fluoride (7.8g, 63.9mmol) in diethyl ether (10mL) to a slurry of lithium aluminum hydride (2.4g) in diethyl ether
10 (100mL) at 0°C. Warm to room temperature and stir for 1 hour. Add water (2.5mL), 5M NaOH (1.9mL) and more water (5mL) with vigorous stirring. Filter and concentrate filtrate to afford a low melting solid. Dissolve in a minimum of pentane, and precipitate by cooling to -78°C. Filter cold, and wash once with cold pentane. (3g, 44%). ^1H -NMR (400 MHz, CDCl_3) δ 4.22 (d, $J_{\text{H-F}} = 48.2\text{Hz}$, 2H), 3.46 (d, $J = 1.0\text{Hz}$, 2H), 0.93 (d, $J =$
15 1.8Hz, 6H).

The compounds of Preparations 428 – 429 may be prepared essentially as described in Preparation 427 except that the reductions are performed at -78°C.

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Preparation 428

3-Fluoro-2-fluoromethyl-2-methyl-propan-1-ol

^1H NMR (400 MHz, CDCl_3) δ 4.40 (ddd, $J = 47.3, 1.3, 1.3\text{Hz}$, 4H), 3.61 (t, $J = 1.3\text{Hz}$, 2H), 0.98 (t, $J = 1.9\text{Hz}$, 3H).

25

Preparation 429

3-Fluoro-2,2-bis-fluoromethyl-propan-1-ol

^1H -NMR (400 MHz, CDCl_3) δ 4.54 (ddd, $J = 47.0, 1.3, 1.3\text{Hz}$, 6H), 3.77 (m, 2H).

Preparation 430

30 (2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

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(2R, 5R)-5-[(1S,2S)-1-Benzylloxy-2-dibenzylamino-3-(3,5-difluoro-phenyl)-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

Beginning with (R)-5-[1-benzylloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-2-hydroxymorpholine-4-carboxylic acid tert-butyl ester and trifluoromethanesulfonic acid 1-fluoromethyl-cyclopentylmethyl ester, the desired compound may be prepared essentially as described in Preparation 306.

MS: $m/z = 773$ $[M+H]^+$

(2R,5R)-5-[(1S,2S)-1-benzylloxy-2-dibenzylamino-3-(3-fluoro-5-propoxy-phenyl)-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester

Beginning with (2R, 5R)-5-[(1S,2S)-1-Benzylloxy-2-dibenzylamino-3-(3,5-difluoro-phenyl)-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester, the desired compound may be prepared essentially as described in Preparation 382.

MS: $m/z = 814$ $[M+H]^+$

(2R,5R)-5-[(1S,2S)-2-amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid *tert*-butyl ester, trifluoromethanesulfonic acid salt

Beginning with (2R,5R)-5-[(1S,2S)-1-benzylloxy-2-dibenzylamino-3-(3-fluoro-5-propoxy-phenyl)-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester, the desired compound may be prepared essentially as described in Preparation 306.

MS: $m/z = 543$ $[M+H]^+$

Acylation

Add acetic anhydride (0.13 mmoles; 12 μ L) to a solution of (2R,5R)-5-[(1S,2S)-2-amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(1-fluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester, trifluorosulfonic acid salt (0.12 mmoles; 0.08 g) and triethylamine (0.36 mmoles; 50 μ L) in 1.5 mL dichloromethane at room temperature and stir for 4h. Concentrate under reduced pressure and

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subject residue to silica gel chromatography, eluting with 2:1 to 1:2 hexane/ethyl acetate gradient to provide the title compound as white solid (50 mg, 70%).

MS: $m/z = 607$ $[M+Na]^+$

- 5 The compounds of Preparations 431 – 433 may be prepared essentially as described in Preparation 430.

| Prep | Compound | MS(ES) |
|------|--|----------------------------------|
| 431 | (2R, 5R)-5-[(1S,2S)-2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(1-difluoromethyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 647 [M+ HCO ₂] |
| 432 | (2R,3S,5R)-5-[(1S,2S)-[2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(4,4-difluoro-cyclohexylmethoxy)-3-methyl-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 617 [M+H] |
| 433 | (2R,5R)-5-[(1S,2S)-[2-Acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 553 [M+H- t-Bu] |

Preparation 434

(2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxy-propyl]-2-
 10 (2-fluoro-1-fluoromethyl-1-methyl-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester
(2R,5R)-5-[(1S,2S)-2-amino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-(2-fluoro-1-fluoromethyl-1-methyl-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester

Beginning with (5R)-5-[(1S,2S)-1-Benzylloxy-3-(3-benzylloxy-5-fluoro-phenyl)-2-dibenzylamino-propyl]-2-hydroxy-morpholine-4-carboxylic acid tert-butyl ester and
 15 trifluoromethanesulfonic acid 2-fluoro-1-fluoromethyl-1-methyl-ethyl ester, the desired compound may be prepared essentially as described in Preparation 306.

MS: $m/z = 493$ $[M+H]^+$

(2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-
 20 (2-fluoro-1-fluoromethyl-1-methyl-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester

Add acetic anhydride (2.13 mmoles; 201.52 μ L) to a solution of (2R,5R)-5-[(1S,2S)-2-amino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-(2-fluoro-1-

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fluoromethyl-1-methyl-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester (2.03 mmoles; 1.00 g) and triethylamine (2.23 mmoles; 311.29 μ L) in 10 mL dichloromethane at 0°C (ice bath) and stir the mixture at 0°C for 1h. Concentrate under reduced pressure and subject residue to silica gel chromatography eluting with 40:60 to 0:100 hexane/ethyl acetate gradient to give the desired compound as white solid (950.00 mg, 87.53%).

MS: $m/z = 557$ $[M+H]^+$

Ether Formation

Beginning with (2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3-fluoro-5-hydroxy-phenyl)-1-hydroxy-propyl]-2-(2-fluoro-1-fluoromethyl-1-methyl-ethoxy)-morpholine-4-carboxylic acid tert-butyl ester and isobutyl iodide, the title compound may be prepared essentially as described in Preparation 421.

MS: $m/z = 613$ $[M+Na]^+$

The compounds of Preparations 435 – 438 may be prepared essentially as described in Preparation 434.

| Prep | Compound | MS(ES) |
|------|--|-----------------|
| 435 | (2R, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxypropyl]-2-(3-fluoromethyl-2-methylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 613 $[M+Na]$ |
| 436 | (2R, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3-fluoro-5-isopropoxy-phenyl)-1-hydroxypropyl]-2-(3-fluoromethyl-2-methylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 599 $[M+Na]$ |
| 437 | (2R, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxypropyl]-2-(3-fluoromethyl-2-methylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 599 $[M+Na]$ |
| 438 | (2R, 5R)-5-[(1S, 2S)-2-acetylamino-3-(3-fluoro-5-isobutoxy-phenyl)-1-hydroxypropyl]-2-(3,3-difluoromethyl-2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 613 $[M+Na]$ |

Preparation 439

N-{(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-hydroxy-benzyl)-2-hydroxy-ethyl}-acetamide

Beginning with 3-{(2S,3S)-2-Amino-3-[(3R,5S,6R)-(6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-3-hydroxy-propyl}-5-fluoro-phenol, the

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title compound may be prepared by reaction with acetic anhydride as described in Preparation 434.

MS(ES): $m/z = 493$ $[M+HCO_2]$

5

Preparation 440

(2R,3S,5R)-5-((1S,2S)-2-Amino-3-[3-(3-methylbutyl)-5-fluorophenyl]-1-hydroxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine

(2R,3S,5R)-5-((1S,2S)-2-Dibenzylamino-3-[3-(3-methylbutyl)-5-fluorophenyl]-1-benzyloxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine

10

Beginning with (2R,3S,5R)-5-((1S,2S)-2-Dibenzylamino-3-[3-bromo-5-fluorophenyl]-1-benzyloxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine, prepared essentially as described in Preparation 306, the desired compound may be prepared essentially as described in Preparation 409.

MS(ES): $m/z = 731.3$ $[M+1]^+$

15

Hydrogenolysis

Beginning with (2R,3S,5R)-5-((1S,2S)-2-Dibenzylamino-3-[3-(3-methylbutyl)-5-fluorophenyl]-1-benzyloxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine, the title compound may be prepared essentially as described in

20

Preparation 421.

MS(ES): $m/z = 461.2$ $[M+1]^+$

Preparation 441

(2R,3S,5R)-5-((1S,2S)-2-Amino-3-[3-(3-methylbutyl)-phenyl]-1-hydroxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine

25

Beginning with (2R,3S,5R)-5-((1S,2S)-2-Dibenzylamino-3-[3-bromo-phenyl]-1-benzyloxy-propyl)-2-(2,2-di-(fluoromethyl)-propoxy)-3-methylmorpholine, prepared essentially as described in Preparation 306, the title compound may be prepared essentially as described in Preparation 440.

MS(ES): $m/z = 443.2$ $[M+1]^+$

30

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Beginning with nitromethane and appropriately substituted benzaldehydes and formylmorpholines, the following compounds may be prepared essentially as described in Preparation 188.

| Prep | Compound | MS (ES) [M+Na] |
|------|--|-------------------|
| 442 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(4-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 443 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-(trifluoromethylthio)phenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 444 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-fluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 445 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(2,4-difluorophenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |
| 446 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-(3-(trifluoromethyl)phenyl)-propyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | |

5 The following compounds may be prepared essentially as described in Preparation 46.

| Prep | Compound | MS (ES) |
|------|--|---------|
| 447 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(4-methyl-tetrahydro-pyran-4-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 633.56 |
| 448 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(bicyclo[2.2.1]hept-1-ylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 629.47 |
| 449 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-methyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 617.46 |
| 450 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 699.46 |
| 451 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethyl-butoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 605.56 |
| 452 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2-dimethyl-pentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 619.61 |
| 453 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-phenyl-cyclopentylmethoxy)-morpholine-4- | 679.61 |

| | | |
|-----|---|--------|
| | carboxylic acid <u>tert</u> -butyl ester | |
| 454 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(2,2,4-trimethyl-pentyloxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 633.52 |
| 455 | (2R,5R)-5-[(1S,2S)-2-Acetylamino-1-benzyloxy-3-(3,5-difluorophenyl)-propyl]-2-(1-methyl-cyclopentylmethoxy)-morpholine-4-carboxylic acid <u>tert</u> -butyl ester | 617.43 |

Preparation 456

N-{(1S,2S)-2-[2-(3R,5S,6R)-5-Ethyl-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-(3-fluoro-5-hydroxy-benzyl)-2-hydroxy-ethyl]-acetamide

Beginning with (3S,5R)-5-[(1S,2S)-1-benzyloxy-2-dibenzylamino-3-(3,5-difluorophenyl)-propyl]-3-ethyl-2-oxomorpholine-4-carboxylic acid tert-butyl ester, the title compound may be prepared essentially as described in Preparation 439.

MS(ES): m/z = 463 (M+H)

10 EXAMPLE 1

N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-((R)-6-ethoxymorpholin-3-yl)-2-hydroxyethyl]-acetamide trifluoroacetate

(2S,5R)-5-[(1S,2S)-2-Acetyl-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester

15 Add triethylamine (0.030 g, 0.30 mmol) and acetic anhydride (0.024 g, 0.23 mmol) to R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.095 g, 0.228 mmol) in tetrahydrofuran (4 mL) at room temperature. Stir 4 hours and dilute with ethyl acetate. Wash with water and saturated aqueous sodium chloride, dry (magnesium sulfate),
20 concentrate and purify (silica gel chromatography, eluting with 20:80 to 100:0 ethyl acetate:hexanes) to give the desired compound (69 mg, 66%).
MS (ES): m/z = 457.2 [M-H]

25 N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-((3R,6S)-6-ethoxymorpholin-3-yl)-2-hydroxyethyl]-
acetamide trifluoroacetate

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Dissolve (R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-ethoxymorpholine-4-carboxylic acid tert-butyl ester (0.060 g, 0.131 mmol) in dichloromethane (5 mL) and add trifluoroacetic acid (0.74 g, 6.5 mmol). Stir at room temperature for 1.5 hours and concentrate to give the title compound (60 mg, 97%).

5 MS (ES): $m/z = 359.2$ [M+H]

EXAMPLE 2

N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(3,3-dimethylbutoxy)-morpholin-3-yl]-2-hydroxyethyl]-acetamide trifluoroacetate

10 Dissolve (2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(3,3-dimethylbutoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.14 g, 0.27 mmol) in trifluoroacetic acid (2 mL) and stir 10 minutes. Concentrate to give the title compound. (0.14 g, 98.8% yield).

MS (ES): 415.3 $m/z =$ [M+H]

15

The compounds of EXAMPLES 3-43 may be prepared essentially as described in EXAMPLE 2.

| EX | Compound | MS (ES) [M+H] |
|-----|---|------------------|
| 3 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6S)-6-(3,3-dimethylbutoxy)-morpholin-3-yl]-2-hydroxyethyl]-acetamide trifluoroacetate | 415.4 |
| 4 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-isobutoxymorpholin-3-yl]-ethyl]-acetamide trifluoroacetate | 387.3 |
| 5 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6S)-6-isobutoxy-morpholin-3-yl]-ethyl]-acetamide trifluoroacetate | 387.3 |
| 6 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(3-methylbutoxy)-morpholin-3-yl]-ethyl]-acetamide trifluoroacetate | 401.4 |
| 7 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6S)-6-(3-methylbutoxy)-morpholin-3-yl]-ethyl]-acetamide trifluoroacetate | 401.3 |
| 8* | N-[(1S,2S)-2-[(3R,6R)-6-Cycloheptylmethoxymorpholin-3-yl]-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 441.2 |
| 9* | N-[(1S,2S)-2-[(3R,6S)-6-Cycloheptylmethoxymorpholin-3-yl]-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 441.2 |
| 10* | N-[(1S,2S)-2-[(3R,6R)-6-(Adamantan-1-ylmethoxy)-morpholin-3-yl]-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 479.2 |
| 11* | N-[(1S,2S)-2-[(3R,6S)-6-(Adamantan-1-ylmethoxy)-morpholin-3-yl]-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 479.2 |

| | | |
|-----|--|-------|
| 12* | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 427.2 |
| 13* | N-[(1S,2S)-2-((3R,6S)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-Difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 427.2 |
| 14 | 5-(R)-[2-(S)-Acetylamino-3-(4-butoxyphenyl)-1-(S)-hydroxypropyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine trifluoroacetate | 451 |
| 15 | 5-(R)-{2-(S)-Acetylamino-1-(S)-hydroxy-3-[4-(3-methylbutoxy)-phenyl]-propyl}-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine trifluoroacetate | 465 |
| 16 | 5-(R)-[2-(S)-Acetylamino-1-(S)-hydroxy-3-(4-propoxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine trifluoroacetate | 437 |
| 17 | 5-(R)-[2-(S)-Acetylamino-1-(S)-hydroxy-3-(4-isobutoxyphenyl)-propyl]-2-(R)-(2,2-dimethylpropoxy)-3-(S)-methylmorpholine trifluoroacetate | 451 |
| 18 | N-{(1S,2S)-1-(3-Chloro-5-fluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide trifluoroacetate | 417.3 |
| 19 | N-[(1S,2S)-2-[(3R,6R)-6-(2,2-Dimethylpropoxy)-morpholin-3-yl]-2-hydroxy-1-(2,3,5-trifluorobenzyl)-ethyl]-acetamide trifluoroacetate | 419.2 |
| 20 | N-[(1S,2S)-2-[(3R,6R)-6-(2,2-Dimethylpropoxy)-morpholin-3-yl]-2-hydroxy-1-(3-trifluoromethoxybenzyl)-ethyl]-acetamide | 449.2 |
| 21 | N-[(1S,2S)-2-[(3R,6R)-6-(2-Cyclohexylethoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 441.2 |
| 22 | N-[(1S,2S)-2-((3R,6R)-6-Cyclopentylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 413.3 |
| 23 | N-[(1S,2S)-2-((3R,6R)-6-Cyclooctylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide trifluoroacetate | 455.3 |
| 24 | N-{1-(3,5-Difluorobenzyl)-2-hydroxy-2-[6-(tetrahydropyran-4-ylmethoxy)-morpholin-3-yl]-ethyl}-acetamide trifluoroacetate | 429.2 |
| 25 | N-{1-(3,5-Difluorobenzyl)-2-hydroxy-2-[6-(4-methylcyclohexylmethoxy)-morpholin-3-yl]-ethyl}-acetamide trifluoroacetate | 441.2 |
| 26 | N-{1-(3,5-Difluorobenzyl)-2-hydroxy-2-[6-(1-methylcyclohexylmethoxy)-morpholin-3-yl]-ethyl}-acetamide trifluoroacetate | 441.2 |
| 27 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-ethylmorpholin-3-yl]-2-hydroxyethyl}-acetamide trifluoroacetate | 429 |
| 28 | N-[(1S,2S)-2-[(3R,6R)-6-(2,2-Dimethylpropoxy)-morpholin-3-yl]-2-hydroxy-1-(3-hydroxybenzyl)-ethyl]-acetamide trifluoroacetate | 381.2 |
| 29 | N-{(1S,2S)-1-(3,5-Dimethylbenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide trifluoroacetate | 393.5 |
| 30 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylbutoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-2-methoxyacetamide trifluoroacetate | 459 |

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| | | |
|----|---|-----|
| 31 | N-[(1S,2S)-2-((3R,5S,6R)-6-Cyclohexylmethoxy-5-methylmorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-3-methoxypropionamide trifluoroacetate | 485 |
| 32 | N-[(1S,2S)-2-((3R,5S,6R)-6-Cyclohexylmethoxy-5-methylmorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2-methoxyacetamide trifluoroacetate | 471 |
| 33 | Cyclopropanecarboxylic acid [(1S,2S)-2-((3R,5S,6R)-6-cyclohexylmethoxy-5-methylmorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide trifluoroacetate | 467 |
| 34 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(Bicyclo[2.1.1]hex-5-ylmethoxy)-5-methylmorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide-Isomer 1 trifluoroacetate | 439 |
| 35 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(Bicyclo[2.1.1]hex-5-ylmethoxy)-5-methylmorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide-Isomer 2 trifluoroacetate | 439 |
| 36 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(3,3-difluoro-2,2-dimethylbutoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl]-acetamide trifluoroacetate | 465 |
| 37 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2-fluoro-ethoxy)-phenyl]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methylmorpholine trifluoroacetate | 441 |
| 38 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-3-[3-(2,2-difluoro-ethoxy)-phenyl]-1-hydroxy-propyl]-2-(2,2-dimethyl-propoxy)-3-methylmorpholine trifluoroacetate | 459 |
| 39 | (2R,3S,5R)-5-[(1S,2S)-2-Acetylamino-1-hydroxy-3-[3-(2-methylbutoxy)-phenyl]-propyl]-2-(2,2-dimethyl-propoxy)-3-methylmorpholine trifluoroacetate | 465 |
| 40 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(1-fluorocyclohex-1-ylmethoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl]-acetamide trifluoroacetate | |
| 41 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(1-fluorocyclopentylmethoxy)-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide trifluoroacetate | 431 |
| 42 | N-[(1S,2S)-1-(3-Fluoro-5-propoxy-benzyl)-2-hydroxy-2-[(3R,6R)-6-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholin-3-yl]-ethyl]-acetamide trifluoroacetate | 509 |
| 43 | N-[(1S,2S)-2-[(3R,6R)-6-(2,2-Dimethyl-4-propoxy-butoxy)-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide trifluoroacetate | 513 |

*78% enantiomeric excess

EXAMPLE 44

Butyric acid (2R,5R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-morpholin-2-ylmethyl ester hydrochloride

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To (R)-5-[(1S,2S)-2-acetylamino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-butyryloxymethyl-morpholine-4-carboxylic acid tert-butyl ester (0.022 g, 0.043 mmol) add 4 M hydrogen chloride in 1,4-dioxane (0.500 mL, 2.00 mmol) and stir for 45 minutes. Concentrate under reduced pressure to give the title compound as an off-white solid (20.0 mg, 100%).

MS (ESI): m/z = 415 [M+H]

The compounds of EXAMPLES 45-67 may be prepared essentially as described in EXAMPLE 44.

| EX | Compound | MS (ES) [M+H] |
|----|---|------------------|
| 45 | 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine hydrochloride | 421 |
| 46 | 5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3-methylbutyl)-morpholine hydrochloride | 421 |
| 47 | 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(3,3-dimethylbutyl)-morpholine hydrochloride | 435 |
| 48 | 5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(3,3-dimethylbutyl)-morpholine hydrochloride | 435 |
| 49 | 5-(R)-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(S)-(4,4-dimethylpentyl)-morpholine hydrochloride | 449 |
| 50 | 5-(S)-[2-(R)-Acetylamino-3-(3,5-difluorophenyl)-1-(R)-hydroxypropyl]-2-(S)-(4,4-dimethylpentyl)-morpholine hydrochloride | 449 |
| 51 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-((3R,6R)-6-phenoxyethylmorpholin-3-yl)-ethyl]-acetamide hydrochloride | 456.0 [M-H] |
| 52 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-((3R,6R)-6-hydroxymethylmorpholin-3-yl)-ethyl]-acetamide hydrochloride | 345.0 |
| 53 | (R)-5-[2-(S)-Acetylamino-3-(3,5-difluorophenyl)-1-(S)-hydroxypropyl]-2-(R)-2-fluorophenoxyethyl-morpholine hydrochloride | 439.3 [M] |
| 54 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexyloxymethylmorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 427.3 [M] |
| 55 | N-[(1S,2S)-2-[(3R,6R)-6-(3-Acetylphenoxyethyl)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 463.0 |
| 56 | (E)-2-Methylbut-2-enedioic acid 1-{[(1S,2S)-2-((3R,6R)-6-cyclohexyloxymethylmorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide} 4-dipropylamide hydrochloride | 580.5 |
| 57 | N-[(1S,2S)-2-[(3R,6R)-6-(4-Acetylphenoxyethyl)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 463.0 |
| 58 | N-[2-[6-(S)-(2-Cyclohexylethyl)-morpholin-3-(R)-yl]-1-(S)-(3,5-difluorobenzyl)-2-(S)-hydroxyethyl]-acetamide hydrochloride | 425.2 |
| 59 | N-[1(S)-(3,5-Difluorobenzyl)-2-(S)-hydroxy-2-(6-(S)-phenethylmorpholin-3-(R)-yl)-ethyl]-acetamide hydrochloride | 419.2 |

| | | |
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| 60 | N-{1-(S)-Benzyl-2-[6-(S)-(2-cyclohexylethyl)-morpholin-3-(R)-yl]-2-(S)-hydroxyethyl}-acetamide hydrochloride | 389.5 |
| 61 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-((R)-6,6-diphenylmorpholin-3-yl)-2-hydroxyethyl]-acetamide hydrochloride | 467.3 |
| 62 | N-[(1S,2S)-2-[(3R,6R)-6-(2,2-Dimethylpropoxy)-morpholin-3-yl]-2-hydroxy-1-(3-trifluoromethylbenzyl)-ethyl]-acetamide hydrochloride | 433 |
| 63 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxy-1-(3-isobutylsulfanylbenzyl)-ethyl]-acetamide hydrochloride | 467 |
| 64 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethylpropoxy)-5-methylmorpholin-3-yl]-1-(3-fluoro-5-isobutylsulfanylbenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 485 |
| 65 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethylpropoxy)-5-methylmorpholin-3-yl]-1-(3-fluoro-5-propylsulfanylbenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 471 |
| 66 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxy-1-(3-propylsulfanylbenzyl)-ethyl]-acetamide hydrochloride | 453 |

EXAMPLE 67

(2R,5R)-2-Cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-((E)-3-dipropylcarbamoyl-2-methylacryloylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid hydrochloride

5

Dissolve (2R,5R)-2-cyclohexylmethoxy-5-[(1S,2S)-3-(3,5-difluorophenyl)-2-((E)-3-dipropylcarbamoyl-2-methylacryloylamino)-1-hydroxypropyl]-morpholine-4-carboxylic acid tert-butyl ester (0.051 g, 0.075 mmol) in trifluoroacetic acid (1.5 mL) and stir at room temperature for 15 minutes. Dilute with dichloromethane (15 mL), concentrate, dissolve in ethyl acetate (30 mL), wash with 1:1 saturated aqueous sodium chloride:saturated aqueous sodium bicarbonate (30 mL), dry (sodium sulfate) and concentrate. Dissolve the residue in ethyl acetate and add 1 M hydrogen chloride in diethyl ether (0.20 mL, 0.20 mmol) and concentrate to give the title compound (0.045 g, 97.3%).

10

MS (ES): m/z = 580.5 [M+H]

15

The compounds of EXAMPLES 68-134 may be prepared essentially as described in EXAMPLE 67.

| EX | Compound | MS (ES) [M+H] |
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| 68 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-3,3,3-trifluoropropionamide hydrochloride | 495.0 [M] |
| 69 | (E)-5,5-Dimethyl-4-oxohex-2-enoic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide | 523.2 [M] |
| 70 | Trans-Cyclopropane-1,2-dicarboxylic acid 1-{[(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide} 2-(methylpropylamide) hydrochloride-Isomer 1 | 552.2 [M] |
| 71 | Trans-Cyclopropane-1,2-dicarboxylic acid 1-{[(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide} 2-(methylpropylamide) hydrochloride-Isomer 2 | 552.2 [M] |
| 72 | (E)-2-Methylbut-2-enedioic acid 1-{[(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide} 4-dimethylamide hydrochloride | 524.0 [M] |
| 73 | (E)-2-Methylbut-2-enedioic acid 1-{[(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide} 4-(methylpropylamide) hydrochloride | 552.2 [M] |
| 74 | (E)-But-2-enedioic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide dipropylamide hydrochloride | 566.5 |
| 75 | (E)-4,4,4-Trifluorobut-2-enoic acid {(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride | 481.0 |
| 76 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6S)-6-(1-fluorocyclohexylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 445.2 |
| 77 | N-[(1S,2S)-2-[(3R,6S)-6-(3- <i>tert</i> -butylcyclobutoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 447.3 |
| 78 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6S)-6-(4-fluorotetrahydropyran-4-ylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 441.2 |
| 79 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 469.0 |
| 80 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 467.3 |
| 81 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(4-methoxycyclohexylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride-Isomer 1 | 457.35 |
| 82 | N-{1-(1SR,2SR)-(3,5-Difluorobenzyl)-2-[(3RS,6RS)-6-(4,4-difluorocyclohexylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 463.22 |
| 83 | N-{1-(1SR,2SR)-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3RS,6RS)-6-(4-methyltetrahydropyran-4-ylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 443.80 |

| | | |
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| 84 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-((3R,6S)-6-[(R)-1-(tetrahydrofuran-2-yl)methoxy]-morpholin-3-yl)-ethyl)-acetamide hydrochloride | 415.23 |
| 85 | N-[(1S,2S)-2-[(3R,6S)-6-(Bicyclo[2.2.1]hept-1-ylmethoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 439.25 |
| 86 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2,2-dimethylpropionamide hydrochloride | 469.40 |
| 87 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxy-morpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-isobutyramide hydrochloride | 455.35 |
| 88 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6S)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-ethyl)-acetamide hydrochloride | 427.21 |
| 89 | N-[(1S,2S)-2-[(3R,6S)-6-((R)-1-Cyclohexylethoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 441.26 |
| 90 | N-[(1S,2S)-2-[(3R,6S)-6-(1-Benzylcyclopentylmethoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 503.40 |
| 91 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6S)-6-(4-oxocyclohexylmethoxy)-morpholin-3-yl]-ethyl)-acetamide hydrochloride | 441.30 |
| 92 | Cyclobutanecarboxylic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride | 467.31 |
| 93 | Cyclopropanecarboxylic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride | 453.20 |
| 94 | Thiophene-2-carboxylic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride | 495.40 |
| 95 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2-methoxyacetamide hydrochloride | 457.40 |
| 96 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2-cyclopropylacetamide hydrochloride | 467.45 |
| 97 | N-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-3,3-dimethylbutyramide hydrochloride | 483.42 |
| 98 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propoxy)-morpholin-3-yl]-ethyl)-acetamide hydrochloride | 509.24 |
| 99 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylbutoxy)-morpholin-3-yl]-2-hydroxyethyl)-acetamide hydrochloride | 415.56 |
| 100 | N-((1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpentyloxy)-morpholin-3-yl]-2-hydroxyethyl)-acetamide hydrochloride | 429.60 |

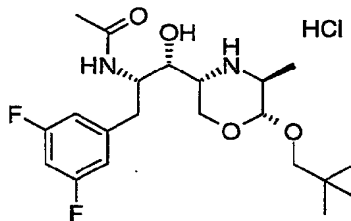
| | | |
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| 101 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(1-phenylcyclopentylmethoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 489.60 |
| 102 | N-[(1S,2S)-2-[(3R,6S)-6-((S)-1-Cyclohexylethoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 441.30 |
| 103 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(2,2,4-trimethylpentylloxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 443.31 |
| 104 | N-[(1S,2S)-2-[(3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-3-methoxypropionamide hydrochloride | 471.4 |
| 105 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 401.2 |
| 106 | N-[(1S,2S)-2-[(3R,6S)-6-Cyclohexyloxymorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 413.3 |
| 107 | (R)-Tetrahydrofuran-2-carboxylic acid [(1S,2S)-2-[(3R,6R)-6-cyclohexylmethoxymorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride | |
| 108 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6S)-6-isobutoxymorpholin-3-yl]-ethyl]-acetamide hydrochloride | 387.2 |
| 109 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-isobutoxymorpholin-3-yl]-ethyl]-acetamide hydrochloride | 387.2 |
| 110 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethylpropoxy)-5-methyl-morpholin-3-yl]-1-(2-ethylbenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 407.3 |
| 111 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 455.3 |
| 112 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-isobutoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 459.5 |
| 113 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 455.3 |
| 114 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-(2-ethyl-butoxy)-5-fluoro-benzyl]-2-hydroxy-ethyl]-acetamide hydrochloride | 497.2 |
| 115 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-fluoro-5-(3-methyl-butoxy)-benzyl]-2-hydroxy-ethyl]-acetamide hydrochloride | 483.3 |
| 116 | N-[(1S,2S)-1-(3-Allyloxy-5-fluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 453.0 |
| 117 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(2,2-Dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-fluoro-5-(2,2,2-trifluoro-ethoxy)-benzyl]-2-hydroxy-ethyl]-acetamide hydrochloride | 495.4 |

| | | |
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| 118 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-4,4-difluoro-6-methylheptanoic acid amide hydrochloride | 535.2 |
| 119 | N-{(1S,2S)-1-(3-butyl-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride-Isomer 2 | 453.3 |
| 120 | N-{(1S,2S)-1-(3-butyl-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride-Isomer 4 | 453.3 |
| 121 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-4,4-difluoro-6-methylheptanoic acid amide hydrochloride | 521.3 |
| 122 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}- <u>trans</u> -2-fluoromethylcyclopropanecarboxylic acid amide hydrochloride-Isomer 1 | 459.2 |
| 123 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}- <u>trans</u> -2-fluoromethylcyclopropanecarboxylic acid amide hydrochloride-Isomer 2 | 459.2 |
| 124 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-5,5,5-trifluoropentanoic acid amide hydrochloride | 497.2 |
| 125 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-4,5,5-trifluoropent-4-enoic acid amide hydrochloride | 495.0 |
| 126 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}- <u>trans</u> -2,2-difluoromethylcyclopropanecarboxylic acid amide hydrochloride-Isomer 1 | 477.0 |
| 127 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}- <u>trans</u> -2,2-difluoromethylcyclopropanecarboxylic acid amide hydrochloride-Isomer 2 | 477.0 |
| 128 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}- <u>cis</u> -cyclopropane-1,2-dicarboxylic acid amide 2-methylpropylamide hydrochloride | 526.2 |
| 129 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-2,2-difluoropropionamide hydrochloride | 451.0 |
| 130 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-2-fluoropropionamide hydrochloride-Isomer 1 | 433.0 |
| 131 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-2-fluoropropionamide hydrochloride-Isomer 2 | 433.0 |
| 132 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-4,4,4-trifluorobutyramide hydrochloride | 483.3 |
| 133 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-4,4,4-trifluoro-2- | 495.2 |

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| | | |
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| | methylbut-2-enoic acid amide hydrochloride | |
| 134 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-3-(dipropylcarbamoyl)-2-methylpropionamide hydrochloride | 556.3 |

EXAMPLE 135



N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride

5 Dissolve (1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol (70 mg, 0.188 mmol) in dry dichloromethane (1.8 mL) under nitrogen. Add dropwise acetic anhydride (22 μ L, 0.233 mmol) and stir for 1 hour. Add 1 M hydrogen chloride in diethyl ether (1 mL) and dilute
10 with benzene. Concentrate and purify (HPLC, eluting with 30% to 70% acetonitrile with 0.1 % hydrochloric acid in water) to give the title compound as a white solid (38 mg, 45%)

MS (ES): m/z = 415.3 [M+H]

15 The compound of EXAMPLE 136-143 may be prepared essentially as described in EXAMPLE 135.

| EX | Compound | MS (ES) [M+H] |
|-----|--|---------------|
| 136 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5R,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 415.3 |
| 137 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-isobutyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 457 |
| 138 | N-[(1S,2S)-2-[(3R,6R)-5-Cyclopropylmethyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 455 |
| 139 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 441 |

| | | |
|-----|---|-----|
| 140 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(1-methyl-cyclopentylmethoxy)-morpholin-3-yl]-ethyl}-2-methoxy-acetamide hydrochloride | 470 |
| 141 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(1-methylcyclopropylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 413 |
| 142 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2-ethyl-2-methylbutoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 443 |
| 143 | N-{(1S,2S)-1-Benzyl-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 379 |

EXAMPLE 144

N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-2-methoxyacetamide hydrochloride

- 5 Dissolve (1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-[(5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-propan-1-ol (31 mg, 0.083 mmol) in dry 1:1 dichloromethane:diethyl ether (1 mL) under nitrogen. Cool to 0 °C and add dropwise methoxyacetyl chloride (7.6 µL, 0.083 mmol). Stir for 1 hour, quench with methanol, concentrate and purify (reverse-phase HPLC, eluting with 10:90 to 50:50
- 10 acetonitrile:water with 8 mM hydrochloric acid), to give the title compound (26 mg, 65%).

MS (ES): m/z = 445.0 [M+H]

- The compounds of EXAMPLES 145-159 may be prepared essentially as
- 15 described in EXAMPLE 144 using the appropriate acid chloride.

| EX | Compound | MS (ES) [M+H] |
|-----|--|------------------|
| 145 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-propionamide hydrochloride | 429.0 |
| 146 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-butyramide hydrochloride | 443.0 |
| 147 | Pentanoic acid {(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride | 457.2 |
| 148 | {(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2- | 431.0 |

| | | |
|-----|--|-------|
| | dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-carbamic acid methyl ester hydrochloride | |
| 149 | {{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-carbamic acid ethyl ester hydrochloride | 445.0 |
| 150 | N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-4-methoxybutyramide hydrochloride | 473.0 |
| 151 | N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-3-methoxypropionamide hydrochloride | 459.0 |
| 152 | N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-3-methylbutyramide hydrochloride | 457.2 |
| 153 | N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-2-phenylacetamide hydrochloride | 491.0 |
| 154 | Cyclopropanecarboxylic acid {{(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride | 441.0 |
| 155 | 3-Methyl-but-2-enoic acid {{(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride | 445.0 |
| 156 | 2-Butoxy-N-{{(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 487.0 |
| 157 | (S)-N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-2-methoxypropionamide hydrochloride | 459.0 |
| 158 | N-{{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-4,4,4-trifluorobutyramide hydrochloride | 497.0 |
| 159 | Furan-2-carboxylic acid {{(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride | 467.0 |

EXAMPLE 160

(E)-2-Methyl-but-2-enoic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride

- 5 To a suspension of (2R,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid tert-butyl ester (30 mg, 0.064 mmol) in dichloromethane (1.6 mL), add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (13 mg, 0.067 mmol), and tiglic acid (6.2 mg in

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300 μ L of dichloromethane). Stir at room temperature for 1.5 hours and purify (silica gel chromatography, eluting from 5:95 to 100:0 ethyl acetate:hexanes) to give the acylated BOC intermediate (30 mg). Dissolve the residue in trifluoroacetic acid (1.1 mL), stir for 15 minutes at room temperature, concentrate and dissolve in ethyl acetate. Wash the solution with saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, dry (sodium sulfate), filter, and concentrate. Dissolve the residue in ethyl acetate (5 mL) add hydrogen chloride (0.14 mL, 1.0 M solution in diethyl ether) and concentrate to give the title compound as a white solid (23 mg).

LC-MS: m/z = 467 $[M+H]^+$, 501 $[M+35]^-$

The compound of EXAMPLE 161 may be prepared essentially as described in EXAMPLE 160 using angelic acid.

| EX | Compound | LC-MS [M+H] |
|-----|---|----------------|
| 161 | (Z)-2-Methyl-but-2-enoic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride | 467 |

EXAMPLE 162

3-[(1S,2S)-2-((3R,6R)-6-Cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-1-hexyl-1-methylurea hydrochloride

Add hexylmethylcarbamic chloride (11 mg, 0.062 mmol) to a solution of (2R,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-cyclohexylmethoxymorpholine-4-carboxylic acid tert-butyl ester (30mg, 0.062mmol) and pyridine (10 μ L, 0.123 mmol) in dichloromethane at 0 °C. Heat to 55 °C for four days. Perform purification, isolation, trifluoroacetic acid deprotection and salt exchange according to the procedure essentially as described for (E)-2-methyl-but-2-enoic acid [(1S,2S)-2-((3R,6R)-6-cyclohexylmethoxymorpholin-3-yl)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-amide hydrochloride.

LC-MS: m/z = 526 $[M+H]^+$, 660 $[M+35]^-$

EXAMPLE 163

Cyclopentanecarboxylic acid {(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)morpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride

(2R,5R)-5-[(1S,2S)-2-(Cyclopentanecarbonylamino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester

Stir cyclopentanecarboxylic acid (0.01 mL, 0.12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.02 g, 0.12 mmol) and 1-hydroxybenzotriazole monohydrate (HOBT) (0.02 g, 0.12 mmol) in dichloromethane (1 mL) at room temperature for 30 minutes. Add (2R,5R)-5-[(1S,2S)-2-amino-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2-(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.05 g, 0.11 mmol) in dichloromethane (1 mL) and triethylamine (0.06 mL, 0.44 mmol) and stir at room temperature overnight. Wash with saturated aqueous sodium bicarbonate, dry (magnesium sulfate), filter, concentrate and purify (silica gel chromatography, eluting with 80:20 hexane:ethyl acetate), to give the desired compound as white solid (0.06 g, 98%).

MS (ES): $m/z = 599$ $[M+HCO_2]^+$

15 Cyclopentanecarboxylic acid {(1S,2S)-1-(3,5-difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethylpropoxy)morpholin-3-yl]-2-hydroxyethyl}-amide hydrochloride

Dissolve (2R,5R)-5-[(1S,2S)-2-(cyclopentanecarbonylamino)-3-(3,5-difluorophenyl)-1-hydroxypropyl]-2(2,2-dimethylpropoxy)-morpholine-4-carboxylic acid tert-butyl ester (0.06 g, 0.11 mmol) in trifluoroacetic acid (1.1 mL, 14.6 mmol) and stir for 15 minutes. Concentrate and add 2 M hydrogen chloride in diethyl ether (0.5 mL, 1 mmol) and concentrate to give the desired compound (0.045 mg, 80%).

MS (ES): $m/z = 455$ $[M+H]^+$

The compounds of EXAMPLES 164-166 may be prepared essentially as described in EXAMPLE 163 using the appropriate acids.

| EX | Compound | MS (ES) [M+H] |
|-----|--|------------------|
| 164 | 2,2-Difluorocyclopropanecarboxylic acid {(1S,2S)-1-(3,5-difluorobenzyl)2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-amide-Isomer 1 | 463 |
| 165 | 2,2-Difluorocyclopropanecarboxylic acid {(1S,2S)-1-(3,5-difluorobenzyl)2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-amide-Isomer 2 | 463 |
| 166 | N-[(1S,2S)-1-(3,5-difluorobenzyl)2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl]-2,2- | 437 |

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| | | |
|-----|---|-----|
| | difluoroacetamide | |
| 167 | 1-Methyl-hexanoic acid {(1S,2S)-1-(3,5-difluorobenzyl)2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-amide-Isomer 1 | 471 |
| 168 | 1-Methylhexanoic acid {(1S,2S)-1-(3,5-difluorobenzyl)2-[(3R,6R)-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-2-hydroxyethyl}-amide-Isomer 2 | 471 |

EXAMPLE 169

N-{(1S,2S)-1-[3-(2,2-Difluoroethoxy)-benzyl]-2-hydroxy-2-[(3R,6R)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride

- 5 Dissolve (2R,5R)-5-{(1S,2S)-2-acetyl-amino-3-[3-(2,2-difluoroethoxy)-phenyl]-1-hydroxypropyl}-2-(1-methylcyclopentylmethoxy)-morpholine-4-carboxylic acid tert-butyl ester (223 mg) in trifluoroacetic acid and stir for 45 minutes and concentrate. Coevaporate three times with dichloromethane (2 mL) and 1 M hydrogen chloride in diethyl ether (1 mL) to give the title compound (213 mg).

10 MS (ES): m/z = 471 [M+H]

The compounds of EXAMPLES 170-224 may be prepared essentially as described in EXAMPLE 169.

| EX | Compound | MS (ES) [M+H] |
|-----|---|------------------|
| 170 | Acetic acid (1S,2S)-2-acetyl-amino-3-[3-(2,2-difluoroethoxy)-phenyl]-1-[(3R,6R)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-propyl ester hydrochloride | 513 |
| 171 | N-[(1S,2S)-2-Hydroxy-2-[(3R,6R)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-1-(3-propoxybenzyl)-ethyl]-acetamide hydrochloride | 449 |
| 172 | Acetic acid (1S,2S)-2-acetyl-amino-1-[(3R,6R)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-3-(3-propoxyphenyl)-propyl ester hydrochloride | 491 |
| 173 | N-{(1S,2S)-1-(3-Benzoyloxybenzyl)-2-hydroxy-2-[(3R,6R)-6-(1-methylcyclopentylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 497 |
| 174 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-propoxybenzyl)-ethyl]-acetamide hydrochloride | 437 |
| 175 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-hydroxybenzyl)-ethyl]-acetamide hydrochloride | 395 |

| | | |
|-----|--|-------|
| 176 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-cyclopentylmethoxybenzyl)-ethyl]-acetamide hydrochloride | 477 |
| 177 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-((S)-2-methyl-butoxy)benzyl)-ethyl]-acetamide hydrochloride | 465 |
| 178 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-ethoxybenzyl)-ethyl]-acetamide hydrochloride | 423 |
| 179 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-allyloxybenzyl)-ethyl]-acetamide hydrochloride | 435 |
| 180 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-(2-fluoroethoxy)benzyl)-ethyl]-acetamide hydrochloride | 441 |
| 181 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-(trifluoromethoxy)benzyl)-ethyl]-acetamide hydrochloride | 463.3 |
| 182 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-(2,2,2-trifluoroethoxy)benzyl)-ethyl]-acetamide hydrochloride | 477.2 |
| 183 | N-[(1S,2S)-2-Hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3-(methoxy)benzyl)-ethyl]-acetamide hydrochloride | 409.5 |
| 184 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6S)-6-(2-fluoro-2-methylpropoxy)-morpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 405 |
| 185 | N-[(1S,2S)-2-[(3R,5S,6R)-5-Butyl-6-(2,2-dimethylpropoxy)-morpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 457 |
| 186 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylpropoxy)-5-(3-fluoropropyl)-morpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 461 |
| 187 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethylbutoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 429 |
| 188 | N-[(1S,2S)-2-[(3R,5S,6R)-6-Cyclohexylmethoxy-5-methylmorpholin-3-yl]-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-acetamide hydrochloride | 441 |
| 189 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(4,4-difluorocyclohexylmethoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 477 |
| 190 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(3-fluoropropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl]-acetamide hydrochloride | 405 |
| 191 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(3,3,3-trifluoropropoxy)-morpholin-3-yl]-ethyl]- | 441 |

| | | |
|-----|---|-------|
| | acetamide hydrochloride | |
| 192 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2-ethylbutoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 429 |
| 193 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(tetrahydropyran-4-ylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 443 |
| 194 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(4,4,4-trifluorobutoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 455 |
| 195 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 483 |
| 196 | N-{(1S,2S)-1-(4-Fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 397.3 |
| 197 | N-{(1S,2S)-1-(3-(Trifluoromethylthio)benzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 479.2 |
| 198 | N-{(1S,2S)-1-(3-Fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 397.2 |
| 199 | N-{(1S,2S)-1-(2,4-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 415.3 |
| 200 | N-{(1S,2S)-1-(3-Trifluoromethylbenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 447.3 |
| 201 | N-{(1S,2S)-1-(3-Trifluoromethylbenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 447.3 |
| 202 | N-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2(R)-methoxy-propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 417.0 |
| 203 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(1-fluoromethylcyclopentylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 445 |
| 204 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(1-fluoromethyl-cyclopentylmethoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 459 |
| 205 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(1-difluoromethyl-cyclopentylmethoxy)-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 463 |
| 206 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(1-trifluoromethylcyclopropylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 467 |

| | | |
|-----|---|-----|
| 207 | N-[(1S,2S)-2-[(3R,6R)-6-(1-Fluoromethyl-cyclopentylmethoxy)-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 485 |
| 208 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(3,3-difluoro-2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 451 |
| 209 | N-[(1S,2S)-2-[(3R,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-(3-fluoro-5-isobutoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 491 |
| 210 | N-[(1S,2S)-1-(3-cyclopentyl-5-fluoro-benzyl)-2-[(3R,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-2-hydroxy-ethyl]-acetamide hydrochloride | 503 |
| 211 | N-[(1S,2S)-2-[(3R,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-(3-fluoro-5-isopropoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 477 |
| 212 | N-[(1S,2S)-2-[(3R,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 477 |
| 213 | N-[(1S,2S)-2-[(3R,6R)-6-(3,3-Difluoro-2,2-dimethyl-propoxy)-morpholin-3-yl]-1-(3-fluoro-5-isobutoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 491 |
| 214 | N-[2-[(3R,6R)-6-(2,2-Bis-(fluoromethyl)-butoxy)-morpholin-3-yl]-(1S,2S)-1-(3,5-difluoro-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 451 |
| 215 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(1-difluoromethyl-cyclopentylmethoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 477 |
| 216 | N-[2-[(3R,5S,6R)-6-(2,2-Bis-(fluoromethyl)-butoxy)-5-methyl-morpholin-3-yl]-(1S,2S)-1-(3,5-difluoro-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 465 |
| 217 | N-[2-[(3R,6R)-6-(1-Difluoromethyl-cyclopentylmethoxy)-morpholin-3-yl]-(1S,2S)-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 503 |
| 218 | N-[2-[(3R,6R)-6-(2,2-Bis-(fluoromethyl)-butoxy)-morpholin-3-yl]-(1S,2S)-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 491 |
| 219 | N-[(1S,2S)-[2-(3R,5S,6R)(6-Cyclopentylmethoxy-5-methyl-morpholin-3-yl)-1-(3,5-difluoro-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 427 |
| 220 | N-[(1S,2S)-[2-(3R,5S,6R)-[6-(4,4-Difluoro-cyclohexylmethoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 517 |
| 221 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(4,4,4-trifluoro-2,2-dimethyl-butoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 469 |
| 222 | N-[(1S,2S)-1-(3-Fluoro-5-propoxy-benzyl)-2-hydroxy-2-[(3R,5S,6S)-5-methyl-6-(2,2,2-trifluoro-ethoxy)-morpholin-3-yl]- | 467 |

| | | |
|-----|---|-----|
| | ethyl}-acetamide hydrochloride | |
| 223 | N-{(1S,2S)-1-(3-Fluoro-5-isobutoxy-benzyl)-2-hydroxy-2-[(3R,5S,6S)-5-methyl-6-(2,2,2-trifluoro-ethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 481 |
| 224 | N-{(1S,2S)-1-[3-(2,2-Difluoro-ethoxy)-5-fluoro-benzyl]-2-hydroxy-2-[(3R,5S,6S)-5-methyl-6-(2,2,2-trifluoro-ethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 489 |

EXAMPLE 225

N-{1-Cyclohexylmethyl-2-[6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide hydrochloride

- 5 Dissolve N-{1-benzyl-2-[6-(2,2-dimethylpropoxy)-5-methylmorpholin-3-yl]-2-hydroxyethyl}-acetamide (21 mg, 0.051 mmol) in glacial acetic acid (5.0 mL) with 30% platinum (IV) oxide (40 mg) in a high pressure reaction vessel. Stir under an atmosphere of 50 psi hydrogen gas overnight. Filter catalyst, concentrate, and purify (reverse phase chromatography, eluting with acetonitrile/0.01 M hydrochloric acid). Lyophilize
- 10 overnight to give the title compound as a white powder (15 mg, 69% yield).
LC-MS: $m/z = 385$ $[M+H]^+$, 383 $[M-H]$

EXAMPLE 226

- N-{(1S,2S)-1-(3-Isopropylsulfanyl-5-fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride
- 15 Cool a solution of (1S,2S)-2-Amino-3-(3-isopropylsulfanyl-5-fluorobenzyl)-1-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol (60 mg, 0.13 mmol) in 1:1 dichloromethane:diethyl ether (1.29 mL) to 0°C. Add acetyl chloride (9 μ L, 0.13 mmol) and stir at 0°C for 1 hour. Dilute reaction mixture with
- 20 methanol and concentrate under a stream of nitrogen. Subject residue to reverse phase HPLC chromatography, eluting with a gradient of 10 – 100% acetonitrile in 0.01 M HCl. Combine desired fractions, freeze, and remove volatiles by lyophilization to provide the title compound as a white powder (20 mg, 28%).

LC-MS: $m/z = 507$ $[M+H]^+$

- 25 The compounds of EXAMPLES 227 – 257 may be prepared essentially as described in EXAMPLE 226.

| EX | Compound | MS (ES) |
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| 227 | N-{(1S,2S)-1-(3-Isopropylsulfanyl-5-fluorobenzyl)-2-hydroxy-2-[(3R,6R)-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 492.8 [M ⁺] |
| 228 | N-{(1S,2S)-1-(3-(2-methylprop-2-yl)sulfanyl-5-fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methyl-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 520.8 [M ⁺] |
| 229 | N-{(1S,2S)-1-(3-(2,2-dimethylpropoxy)-5-fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methyl-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 519.3 [M ⁺ +H] |
| 230 | N-{(1S,2S)-1-(3-isobutoxy-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(3-fluoro-2,2-dimethylpropoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 487.3 [M ⁺ +H] |
| 231 | N-{(1S,2S)-1-(3-cyclopropylmethoxy-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(3-fluoro-2,2-dimethylpropoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 485.0 [M ⁺ +H] |
| 232 | N-{(1S,2S)-1-(3-cyclobutoxy-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 502.8 [M ⁺ +H] |
| 233 | N-{(1S,2S)-1-(3-propoxy-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(2,2,2-tri-(fluoromethyl)ethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 509.3 [M ⁺ +H] |
| 234 | N-{(1S,2S)-1-(3-propoxy-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(trimethylsilylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 471 [M ⁺ +H] |
| 235 | N-{(1S,2S)-1-(3-phenylsulfanyl-5-fluorobenzyl)-2-hydroxy-2-(3R,5S,6R)-5-methyl-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 441.0 [M ⁺ +H] |
| 236 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-1-(3-trifluoromethoxy-benzyl)-ethyl]-acetamide hydrochloride | 499.3 [M ⁺] |
| 237 | Pentanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 457.39 [M ⁺] |
| 238 | N-{(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-3-methoxy-propionamide hydrochloride | 459.29 [M ⁺] |
| 239 | 5-Methyl-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 485.7 [M ⁺] |
| 240 | Octanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 499.9 [M ⁺] |
| 241 | Heptanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 485.56 [M ⁺] |
| 242 | 4-Methyl-pentanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2- | 471.36 [M ⁺] |

| | | |
|-----|---|-----------------------------|
| | hydroxy-ethyl}-amide hydrochloride | |
| 243 | Cyclobutanecarboxylic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 455.39 [M ⁺] |
| 244 | Cyclohexanecarboxylic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 483.34 [M ⁺] |
| 245 | 2-Cyclopentyl-N-[(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 483.35 [M ⁺] |
| 246 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-3,3-dimethyl-butyramide hydrochloride | 471.47 [M ⁺] |
| 247 | Cyclopentanecarboxylic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 469.38 [M ⁺] |
| 248 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-isobutyramide hydrochloride | 443.39 [M ⁺] |
| 249 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid butyl ester hydrochloride | 473.34 [M ⁺] |
| 250 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid isopropyl ester hydrochloride | 459.31 [M ⁺] |
| 251 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid pentyl ester hydrochloride | 487.34 [M ⁺] |
| 252 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid propyl ester hydrochloride | 459.38 [M ⁺] |
| 253 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-propyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 443.0 [M+H] |
| 254 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-propyl-morpholin-3-yl]-2-hydroxy-ethyl]-propionamide hydrochloride | 457.2 [M+H] |
| 255 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-propyl-morpholin-3-yl]-2-hydroxy-ethyl]-2-methoxy-acetamide hydrochloride | 473.2 [M+H] |
| 256 | N-{1-[3-(2,2-Dimethyl-propoxy)-5-fluoro-benzyl]-2-[6-(3-fluoro-2,2-bis-fluoromethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide hydrochloride | 537 [M+H] |
| 257 | N-{1-[3-(3,5-difluorobenzyl)-2-[6-(1-methylcyclobutylmethoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 427 [M+H] |

EXAMPLE 258

N-{(1S,2S)-1-(3-Propylsulfanyl-5-fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(2,2-di-(fluoromethyl)propoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride

Cool a solution of (1S,2S)-2-Amino-3-(3,5-difluorobenzyl)-1-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)propoxy)-5-methylmorpholin-3-yl]-propan-1-ol (148 mg, 0.33 mmol) in dichloromethane (3.29 mL) to 0°C. Add N-acetyl imidazole (43 mg, 0.39 mmol) and triethylamine (91 µL, 0.65 mmol). Allow reaction mixture to warm to room temperature and stir over night. Dilute reaction mixture with dichloromethane and add 1N KH₂PO₄. Wash organic phase with 1N KH₂PO₄, dry over sodium sulfate, and concentrate under reduced pressure. Subject residue to reverse phase HPLC chromatography, eluting with a gradient of acetonitrile (10-100%) in 0.01 M HCl to provide 50 mg (29%) of the title compound.

MS(ES): $m/z = 493.3$ [$M^+ + H$]

The compounds of EXAMPLES 259 – 260 may be prepared essentially as described in EXAMPLE 258.

| EX | Compound | MS (ES) |
|-----|--|----------------|
| 259 | {(1S,2S)-1-(3-(3-methylbutyl)-benzyl)-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide hydrochloride | 485.3 [M+H] |
| 260 | {(1S,2S)-1-(3-(3-methylbutyl)-5-fluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide hydrochloride | 503.3 [M+H] |

EXAMPLE 261

N-{(1S,2S)-1-(3-Propoxy-5-fluorobenzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-(3-fluoro-2,2-dimethylpropoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride

Stir a solution of (2R,3S,5R)-5-[(1S,2S)-1-Hydroxy-2-acetylamino-3-(3-propoxy-5-fluorophenyl)-propyl]-2-(3-fluoro-2,2-dimethylpropoxy)-3-methylmorpholine-4-carboxylic acid *tert*-butyl ester (175 mg) in trifluoroacetic acid (5 mL) for 30 minutes at room temperature. Concentrate under a stream of nitrogen and subject the residue to reverse phase HPLC, eluting with 10-100% acetonitrile in 0.01 M HCl, to provide the title compound.

MS(ES): $m/z = 473$ [$M^+ + H$]

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EXAMPLE 262

3-Methoxypropionic acid {(1S,2S)-1-(3-cyclopropylmethoxy-5-fluorobenzyl)-2-
 [(3R,5S,6R)-5-methyl-6-(3-fluoro-2,2-dimethylpropoxy)-morpholin-3-yl]-2-
 5 hydroxyethyl}-amide hydrochloride

Add 3-methoxypropionic acid (30 μ L, 0.322 mmol), EDCI (93 mg, 0.484 mmol),
 and HOBT (65 mg, 0.484 mmol) to a solution of (1S,2S)-2-amino-3-(3-cyclopropyl-
 methoxy-5-fluorophenyl)-1-(3R,5S,6R)-6-(3-fluoro-2,2-dimethylpropoxy)-5-methyl-
 morpholin-3-yl]-propan-1-ol (138.2 mg, 0.322 mmol) in tetrahydrofuran 5 mL and stir at
 10 room temperature for 3 hours. Dilute the reaction mixture with ethyl acetate, and wash
 with 1.0 N HCl followed by saturated aqueous sodium chloride. Dry the organic phase
 with magnesium sulfate and concentrate under reduced pressure. Subject the residue to
 reverse phase chromatography, eluting with 10-40% acetonitrile in 0.001 N HCl to
 provide the title compound.

15 MS(ES): $m/e = 529.3$ ($M^+ + H$)

The compounds of EXAMPLES 263 – 273 may be prepared essentially as
 described in EXAMPLE 262.

| EX | Compound | MS (ES) |
|-----|--|---------------------|
| 263 | 5,5-Dimethyl-4-oxo-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 513.57 [M^+] |
| 264 | (E)-2-Methyl-hex-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 483.37 [M^+] |
| 265 | (R)-N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-2-methoxy-propionamide hydrochloride | 459.33 [M^+] |
| 266 | Hex-5-ynoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 467.33 [M^+] |
| 267 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-2-ethoxy-acetamide hydrochloride | 459.37 [M^+] |
| 268 | Pent-4-ynoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 453.36 [M^+] |
| 269 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-3-ethoxy-propionamide hydrochloride | 473.35 [M^+] |

| | | |
|-----|---|-----------------------------|
| 270 | 6-Methyl-4-oxo-heptanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 513.36 [M ⁺] |
| 271 | N-{(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-2-propoxy-acetamide hydrochloride | 473.35 [M ⁺] |
| 272 | 4-Cyclopentyl-N-{(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-4-oxo-butyramide hydrochloride | 525.32 [M ⁺] |
| 273 | 5,5-Dimethyl-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 499.33 [M ⁺] |

The compounds of EXAMPLES 274 – 324 may be prepared essentially as described in EXAMPLE 67.

| EX | Compound | MS (ES) |
|-----|---|------------------------------|
| 274 | N-{(1S,2S)-1-(3-Bromo-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 476.0 [M ⁺ +H] |
| 275 | N-{(1S,2S)-1-(3-Propyl-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 439.3 [M ⁺ +H] |
| 276 | N-{(1S,2S)-1-(3-(3-Methylbutyl)-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 467.5 [M ⁺ +H] |
| 277 | N-{(1S,2S)-1-(3-(2-Ethoxyphenyl)-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 517.3 [M ⁺ +H] |
| 278 | N-{(1S,2S)-1-(4-Methyl-3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 429.0 [M ⁺ +H] |
| 279 | N-{(1S,2S)-1-(4-(3-methylbutyl)-3,5-difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-di-(fluoromethyl)-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 485.3 [M ⁺ +H] |
| 280 | N-{(1S,2S)-1-(3-Butyl-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide hydrochloride | 453.3 [M ⁺ +H] |
| 281 | N-{(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-6-methyl-4,4-difluoroheptanoic acid amide hydrochloride | 535.2 [M ⁺ +H] |
| 282 | N-{(1S,2S)-1-(3-Butyl-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-6-methyl-4,4-difluoroheptanoic acid amide hydrochloride | 573.3 [M ⁺ +H] |
| 283 | N-{(1-(3-Bromo-5-fluorobenzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxyethyl}-acetamide | 475.0 [M ⁺ +H] |

| | | |
|-----|---|------------------------------|
| | hydrochloride | |
| 284 | N-[(1S,2S)-1-(3,5-Difluorobenzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxyethyl]-6-methyl-heptanoic acid amide hydrochloride | 485.2 [M ⁺ +H] |
| 285 | N-[(1S,2S)-2-[(3R,6R)-6-Cyclohexylmethoxy-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 467.3 [M ⁺] |
| 286 | N-[(1S,2S)-2-[(3R,6R)-6-Cyclohexylmethoxy-morpholin-3-yl]-1-(3-fluoro-5-isobutoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 481.2 [M ⁺] |
| 287 | N-[(1S,2S)-2-[(3R,6R)-6-Cyclohexylmethoxy-morpholin-3-yl]-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 507.3 [M ⁺] |
| 288 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,5S,6R)-5-methyl-6-((S)-2-methyl-butoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 415.6 [M ⁺] |
| 289 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(4-methyl-tetrahydro-pyran-4-ylmethoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 443.8 [M ⁺] |
| 290 | N-[(1S,2S)-2-[(3R,6R)-6-(Bicyclo[2.2.1]hept-1-ylmethoxy)-morpholin-3-yl]-1-(3,5-difluoro-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 439.25 [M ⁺] |
| 291 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(1-methyl-cyclopentylmethoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 427.21 [M ⁺] |
| 292 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 509.24 [M ⁺] |
| 293 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-butoxy)-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 415.56 [M ⁺] |
| 294 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-pentyloxy)-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride | 429.6 [M ⁺] |
| 295 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(1-phenyl-cyclopentylmethoxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 489.6 [M ⁺] |
| 296 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(2,2,4-trimethyl-pentyloxy)-morpholin-3-yl]-ethyl]-acetamide hydrochloride | 443.31 [M ⁺] |
| 297 | Octanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 485.7 [M ⁺] |
| 298 | 5-Methyl-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 471.9 [M ⁺] |
| 299 | 2,5-Dimethyl-furan-3-carboxylic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2- | 481.34 [M ⁺] |

| | | |
|-----|--|--------------------------|
| | hydroxy-ethyl}-amide hydrochloride | |
| 300 | Heptanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 471.39 [M ⁺] |
| 301 | (E)-2-Methyl-but-2-enedioic acid 4-({(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide) 1-(methyl-propyl-amide) hydrochloride | 526.9 [M ⁺] |
| 302 | N-({(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-N'-methyl-N'-propyl-succinamide hydrochloride | 514.9 [M ⁺] |
| 303 | (E)-2-Methyl-hex-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 469.7 [M ⁺] |
| 304 | 5,5-Dimethyl-4-oxo-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 499.68 [M ⁺] |
| 305 | N-({(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-N'-ethyl-N'-propyl-succinamide hydrochloride | 528.35 [M ⁺] |
| 306 | N-({(1S,2S)-1-(3,5-Difluoro-benzyl)-2-hydroxy-2-[(3R,6R)-6-(1-methyl-cyclopentylmethoxy)-morpholin-3-yl]-ethyl}-acetamide hydrochloride | 427.33 [M ⁺] |
| 307 | Furan-2,5-dicarboxylic acid 2-({(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide)-5-(methyl-propyl-amide) hydrochloride | 552.41 [M ⁺] |
| 308 | 4-Methyl-pentanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 457.4 [M ⁺] |
| 309 | 6-Methyl-4-oxo-heptanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 499.33 [M ⁺] |
| 310 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid pentyl ester hydrochloride | 473.33 [M ⁺] |
| 311 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid butyl ester hydrochloride | 459.32 [M ⁺] |
| 312 | 5-tert-Butyl-2-methyl-furan-3-carboxylic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 523.37 [M ⁺] |
| 313 | 4-Oxo-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 471.35 [M ⁺] |
| 314 | (E)-3,5,5-Trimethyl-4-oxo-hex-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 511.33 [M ⁺] |

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| | | |
|-----|---|-----------------------------|
| 315 | (E)-2-Methyl-oct-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 497.36 [M ⁺] |
| 316 | N-[(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl]-N',N'-dipropyl-succinamide hydrochloride | 542.55 [M ⁺] |
| 317 | {(1S,2S)-1-(3,5-Difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-carbamic acid hexyl ester hydrochloride | 487.37 [M ⁺] |
| 318 | (E)-2-Methyl-4-oxo-hept-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 497.33 [M ⁺] |
| 319 | 4-Cyclopentyl-N-[(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl]-4-oxo-butyramide hydrochloride | 511.32 [M ⁺] |
| 320 | 5,5-Dimethyl-hexanoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 485.32 [M ⁺] |
| 321 | (E)-2,4,4-Trimethyl-hept-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 511.4 [M ⁺] |
| 322 | (E)-2,5-Dimethyl-hex-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 483.2 [M+H] |
| 323 | (E)-6,6,6-Trifluoro-2-methyl-hex-2-enoic acid {(1S,2S)-1-(3,5-difluoro-benzyl)-2-[(3R,6R)-6-(2,2-dimethyl-propoxy)-morpholin-3-yl]-2-hydroxy-ethyl}-amide hydrochloride | 523.0 [M+H] |

EXAMPLE 324

N-[(1S,2S)-1-(3-Cyclopropylmethoxy-benzyl)-2-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl]-acetamide hydrochloride

- 5 Add diisopropylethylamine (0.003 mL) to an ice cold solution of acetic anhydride (0.0018 mL) and (1S,2S)-2-amino-3-(3-cyclopropylmethoxy-phenyl)-1-[(3R,5S,6R)-6-(2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-propan-1-ol trifluoroacetate (9 mg). Stir 2 hours and add saturated aqueous sodium bicarbonate. Wash organic layer with 1N aqueous hydrochloric acid, dry with magnesium sulfate and filter. Add 1N hydrogen
- 10 chloride in ether (0.05 mL) and evaporate to give the title compound (5.5 mg). MS(ESI): $m/z = 449$ [M+H]⁺.

EXAMPLE 325

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N-{(1S,2S)-1-(3-Cyclopropylmethoxy-5-fluoro-benzyl)-2-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide hydrochloride

- Add acetic anhydride (0.040 mL, 0.428 mmol) to an ice cold solution of (1S,2S)-
 5 2-amino-3-(3-cyclopropylmethoxy-5-fluoro-phenyl)-1-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-propan-1-ol (187 mg, 0.41 mmol) and stir 45 minutes. Add aqueous 1N hydrochloric acid, back extract with dichloromethane, wash with saturated sodium chloride, dry with magnesium sulfate and
 10 purify on C-18 reversed phase silica gel with acetonitrile/water/trifluoroacetic acid mixtures. Combine fractions and remove acetonitrile by evaporation. Lyophilize for 18 hours and dissolve in dichloromethane and add 1N hydrogen chloride (0.25 mL) in diethyl ether and evaporate. Coevaporate twice with 1N hydrogen chloride (0.25 mL) in diethyl ether to give the title compound (106 mg). MS(ESI): $m/z = 503$ $[M+H]^+$.

- 15 The compounds of EXAMPLES 326 – 330 may be prepared essentially as described in EXAMPLE 325.

| EX | Compound | MS (ES) |
|-----|---|------------------|
| 326 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-isobutoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride | 505 $[M+H]^+$ |
| 327 | N-{(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-fluoro-5-(2-methyl-cyclopropylmethoxy)-benzyl]-2-hydroxy-ethyl}-acetamide hydrochloride | 517 $[M+H]^+$ |
| 328 | N-{(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-fluoro-5-(1-methyl-cyclopropylmethoxy)-benzyl]-2-hydroxy-ethyl}-acetamide hydrochloride | 517 $[M+H]^+$ |
| 329 | N-{(1S,2S)-1-[3-(1-Cyclopropyl-ethoxy)-5-fluoro-benzyl]-2-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-2-hydroxy-ethyl}-acetamide trifluoroacetate | 517 $[M+H]^+$ |
| 330 | N-[(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-hydroxy-benzyl)-2-hydroxy-ethyl]-acetamide trifluoroacetate | 449 $[M+H]^+$ |

EXAMPLE 331

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N-[2-[6-(3-Fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-propoxy-benzyl)-2-hydroxy-ethyl]-acetamide hydrochloride

Add triethyl amine (0.025mL) and acetic anhydride (0.013mL) to a solution of 5-[2-amino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (67mg) in dichloromethane (2mL). Stir at room temperature for 2 hours. Concentrate under reduced pressure and subject to silica gel chromatography, eluting with a linear gradient from hexanes to ethyl acetate to afford 5-[2-acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (49mg, 68%)

MS: $m/z = 591$ $[M+H^+]$

Dissolve 5-[2-acetylamino-3-(3-fluoro-5-propoxy-phenyl)-1-hydroxy-propyl]-2-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-3-methyl-morpholine-4-carboxylic acid tert-butyl ester (49mg) in trifluoroacetic acid (1mL), stir at ambient temperature for 20 minutes and concentrate under reduced pressure. Dissolve residue in DMSO and purify by reverse-phase chromatography eluting from 10% acetonitrile in 0.01M HCl to 100% acetonitrile. Collect and evaporate the appropriate fractions, then precipitate the residue by adding diethyl ether, and drying under vacuum to afford the title compound (9.5mg). LCMS: $m/z = 491$ $[M+H^+]$

EXAMPLE 332

N-{(1S,2S)-1-(3-cyclopentyloxy-5-fluoro-benzyl)-2-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-2-hydroxy-ethyl}-acetamide hydrochloride

Stir a suspension of N-{(1S,2S)-1-(3-hydroxy-5-fluoro-benzyl)-2-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-2-hydroxy-ethyl}-acetamide (211.83 μ moles; 95.00 mg), bromocyclopentane, (423.65 μ moles; 45.45 μ L;) and cesium carbonate (635.48 μ moles; 207.05 g) in dimethylformamide (1.06 mL) in a sealed tube at 90°C for 1h. Add water and extract with ethyl acetate. Dry the combined organic layers over $MgSO_4$, filter, and concentrate under reduced pressure. Subject residue to silica gel chromatography, eluting with 1% to 5% 7N NH_3 in MeOH/dichloromethane gradient, to provide the free base of the title compound as a pale yellow

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solid. Add 2M HCl in diethyl ether (2 mL) to the free base and remove solvent under vacuum to provide the title compound.

MS(ES): $m/z = 517$

The compounds of EXAMPLES 333 – 334 may be prepared essentially as described in EXAMPLE 332.

| EX | Compound | MS (ES) |
|-----|--|--------------|
| 333 | N-{(1S,2S)-2-[(3R,5S,6R)-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-5-methyl-morpholin-3-yl]-1-(3-fluoro-5-isopropoxy-benzyl)-2-hydroxy-ethyl}-acetamide hydrochloride | 491 [M+H] |
| 334 | N-{(1S,2S)-2-(3R,5S,6R)-[5-Ethyl-6-(3-fluoro-2-fluoromethyl-2-methyl-propoxy)-morpholin-3-yl]-1-[3-fluoro-5-(2-fluoro-ethoxy)-benzyl]-2-hydroxy-ethyl}-acetamide hydrochloride | 509 [M+H] |

EXAMPLE 335

N-{(1S,2S)-2-[(3R,5S,6R)-6-(3-Fluoro-2,2-dimethyl-propoxy)-5-methyl-morpholin-3-yl]-1-[3-fluoro-5-(2-fluoro-ethoxy)-benzyl]-2-hydroxy-ethyl}-acetamide hydrochloride

The title compound may be prepared essentially as described in EXAMPLE 261.

MS(ES): $m/z = 476.8$ [M⁺+H]

The compounds of Formula I are inhibitors of BACE and thereby inhibit the production of A- β peptide which has been implicated in the pathology and progression of a number of neurodegenerative disorders, including Alzheimer's disease (See: Varghese, *et al.*, *Journal of Medicinal Chemistry*, **46**(22), 4625 (2003)). Methods for determining the BACE inhibitory activity of compounds are well known in the art (See: Sinha, *et al.*, *Science*, **286**, 735 (1999); Turner, *et al.*, *Biochemistry*, **40**, 10001 (2001); Hom, *et al.*, *Journal of Medicinal Chemistry*, **46**, 1799 (2003); US #5,744,346; US #5,942,400; WO00/17369; WO00/03819; WO 03/040096; and WO 04/024081).

In vitro Assay Procedures:

For in vitro enzymatic and cellular assays, test compounds are prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted (in a 1:3, 1:2.5, 1:2, or 1:1 dilution series) in DMSO to obtain a final compound concentration of 10 millimolar to 1 micromolar at the first highest concentration of a ten-point dilution curve

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in a 96-well round-bottom plate right before conducting the in vitro enzymatic and whole assays.

In vitro protease inhibition assays:

BACE1 mcaFRET Assay

- 5 Serial dilutions of test compounds are prepared as described above. Two microliter of each dilution is added to each well on row A to H of a corresponding low protein binding black plate to which 50 microliter of 50 millimolar ammonium acetate, pH 4.6, 1 mM Triton X-100, 1mg/ml Bovine Serum Albumin, and 15 micromolar of FRET substrate (sequence: (MCA)-S-E-V-N-L-D-A-E-F-R-K(Dnp)-R-R-R-R-NH₂) for
- 10 BACE1 activity are pre-added. The content is mixed well on a plate shaker for 10 min. Fifty microliter of two hundred picomolar human BACE1(1-460):Fc (See: Vasser, *et al.*, *Science*, **286**, 735-741 (1999)) in the same reaction buffer described above is added to the plate containing substrate and test compounds to initiate the reaction. The relative fluorescence unit (RFU) of the mixture at time 0 is recorded at excitation wavelength
- 15 330nm and emission wavelength 400nm, after brief mixing on a plate shaker. The reaction plate is covered with aluminum foil and kept in a dark humidified oven at room temperature for 16 to 24 hours. The RFU at the end of incubation is recorded with the same excitation and emission settings. The difference of the RFU at time 0 and the end of incubation represents the activity of BACE1 under the compound treatment. The 10-
- 20 point inhibition curve was plotted and fitted with the four-parameter logistic equation to obtain the EC₅₀ and IC₅₀ values. (See: Sinha, *et al.*, *Nature*, **402**, 537-540 (2000)). The exemplified compounds of Formula I were tested essentially as described above and exhibited an IC₅₀ value for BACE1 of lower than 15 μ M. The following exemplified compounds were tested essentially as described above and exhibited the following
- 25 activity for BACE1:

| EXAMPLE | BACE1 IC ₅₀ (nM) |
|---------|-----------------------------|
| 10 | 270 |
| 12 | 110 |
| 67 | 2.8 |

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| | |
|-----|----|
| 135 | 78 |
|-----|----|

BACE2 mcaFRET Assay

Serial dilutions of test compounds are prepared as described above. Two microliter of each dilution is added to each well on row A to H of a corresponding low protein binding black plate to which 50 microliter of 50 millimolar ammonium acetate, pH 4.6, 1 mM Triton X-100, 1mg/ml Bovine Serum Albumin, and 15 micromolar of FRET substrate (sequence: (MCA)-S-E-V-N-L-D-A-E-F-R-K(Dnp)-R-R-R-R-NH₂) for BACE2 activity are pre-added. The content is mixed well on a plate shaker for 10 min. Fifty microliter of four hundred picomolar purified recombinant human BACE2(1-460):Fc in the same reaction buffer described above is added to the plate containing substrate and test compounds to initiate the reaction. The relative fluorescence unit (RFU) of the mixture at time 0 is recorded at excitation wavelength 330nm and emission wavelength 400nm, after brief mixing on a plate shaker. The reaction plate is covered with aluminum foil and kept in a dark humidified oven at room temperature for 16 to 24 hours. The RFU at the end of incubation is recorded with the same excitation and emission setting. The difference of the RFU at time 0 and the end of incubation represents the activity of BACE2 under the compound treatment. The 10-point inhibition curve was plotted and fitted with the four-parameter logistic equation to obtain the EC₅₀ and IC₅₀ values. For example, the BACE2 IC₅₀ value for the compound of EXAMPLE 135 is 220 nM, representing approximately a 3 fold selectivity for BACE1 inhibition.

20 Expression of human BACE1 and human BACE2.

Human (accession number: AF190725) BACE1 and human BACE2 (accession number: AF 204944) were cloned from total brain cDNA by room temperature-PCR. The nucleotide sequences corresponding to amino acid sequences #1 to 460 were inserted into the cDNA encoding human IgG₁ (Fc) polypeptide (Vassar et al. 1999). This fusion protein of BACE1(1-460) or BACE2(1-460) and human Fc, named *huBACE1:Fc* and *huBACE2:Fc* respectively, were constructed into the pJB02 vector. Human BACE1(1-460):Fc (*huBACE1:Fc*) and human BACE2(1-460):Fc (*huBACE2:Fc*) were transiently expressed in HEK293 cells. 250 µg cDNA of each construct was mixed with Fugene 6

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and added to 1 liter HEK293 cells. Four days after the transfection, conditioned media were harvested for purification.

Purification of *huBACE1:Fc* and *huBACE2:Fc*.

5 Conditioned media of HEK293 cell transiently transfected with *huBACE1:Fc* or *huBACE2:Fc* cDNA were collected. Cell debris was removed by filtering the conditioned media through 0.22 μ m sterile filter. 5 ml Protein A-agarose (bed volume) was added to 4 liter conditioned media. This mixture was gently stirred overnight at 4° C. The Protein A-agarose resin was collected and packed into a low-pressure
10 chromatography column. The column was washed with 20X bed volumes of PBS at flow rate 20 ml per hour. Bound *huBACE1:Fc* or *huBACE2:Fc* protein was eluted with 50 mM acetic acid, pH 3.6, at flow rate 20 ml per hour. 1 ml fractions of eluate were neutralized immediately with 0.5 ml 200 mM ammonium acetate, pH 6.5. The purity of final product was assessed by electrophoresis in 4-20% Tris-Glycine SDS-PAGE. The
15 enzyme was stored at -80C in small aliquots.

Whole cell assay for measuring the Inhibition of Beta-Secretase Activity

The routine whole cell assay for the measurement of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEK293p (ATCC Accession No. CRL-1573) stably expressing a human APP751 cDNA containing the naturally occurring
20 double mutation Lys651Met52 to Asn651Leu652, commonly called the Swedish mutation (noted HEK293/APP751sw) and shown to overproduce Abeta (Citron et al., 1992, *Nature* 360:672-674). Human embryonic kidney HEK293p cells stably expressing wild-type human APP751 cDNA (noted HEK293/APP751wt) are also used to assess the inhibition of beta-secretase activity. *In vitro* A β reduction assays have been described in
25 the literature (See: Dovey, et al., *Journal of Neurochemistry*, 76, 173-181 (2001); Seubert, et al., *Nature*, 361, 260 (1993); and Johnson-Wood, et al., *Proc. Natl. Acad. Sci. USA*, 94, 1550-1555 (1997))

Cells (HEK293/APP751sw or HEK293/APP751wt, at 3×10^4 cells/well, containing 200 microliters culture media, DMEM containing 10% FBS) are incubated at 37C for 4 to
30 6 hours in the presence/absence of inhibitors (diluted in DMSO) at the desired

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concentration. At the end of the incubation, conditioned media are analyzed for beta-secretase activity, for example, by analysis of Abeta peptides designated A β 1-x. Abeta peptides are measured by a sandwich ELISA, using monoclonal 266 as a capture antibody and biotinylated 3D6 as reporting antibody. In addition, other APP cleavage fragments, such as sAPPbeta, the cleavage product of full length APP by BACE1, can be measured in conditioned medium to assess beta-secretase activity. The sAPPbeta fragments are analyzed by a sandwich ELISA, using monoclonal 8E5 antibody as a capture antibody and rabbit polyclonal 192sw or 192wt as a reporting antibody. The concentration of Abeta or sAPPbeta released in the conditioned media following the compound treatment corresponds to the activity of BACE1 under such conditions. The 10-point inhibition curve was plotted and fitted with the four-parameter logistic equation to obtain the EC₅₀ and IC₅₀ values for the Abeta, sAPPbeta-lowering effect. The following exemplified compounds were tested essentially as described above and exhibited the following activity for Abeta lowering effect:

| EXAMPLE | IC ₅₀ (nM) |
|---------|-----------------------|
| 10 | 780 |
| 12 | 340 |
| 67 | 32 |
| 135 | 95 |

15 **In vivo Inhibition of Beta-Secretase**

Several animal models, including mouse, guinea pig, dog, and monkey, may be used to screen for inhibition of beta- secretase activity in vivo following compound treatment. Animals used in this invention can be wild type, transgenic, or gene knockout animals. For example, the PDAPP mouse model, prepared as described in Games et al., 1995, *Nature* 373:523-527, and other non-transgenic or gene knockout animals are useful to analyze in vivo inhibition of Abeta and sAPPbeta production in the presence of inhibitory compounds. Generally, 2 to 12 month old PDAPP mice, gene knockout mice or non-transgenic animals are administered compound formulated in vehicles, such as corn oil, cyclodextran, phosphate buffers, Pharmasolve, or other suitable vehicles. One to twenty-four hours following the administration of compound, animals are sacrificed, and

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brains as well as cerebrospinal fluid and plasma are removed for analysis of Abeta and sAPP fragments. (See: Dovey, et al., Journal of Neurochemistry, **76**, 173-181 (2001); and Johnson-Wood, et al., Proc. Natl. Acad. Sci. USA, **94**, 1550-1555 (1997))

Beginning at time 0, animals are administered by oral gavage or other means of
5 delivery, such as sub-cutaneous injection of an inhibitory compound up to 100 mg/kg in a standard formulation such as 7% Pharmasolve. A separate group of animals receive Pharmasolve alone and serve as a vehicle-control group. At the end of the test period, animals are sacrificed and brain tissues, plasma or cerebrospinal fluid are analyzed for the presence of Abeta peptide and sAPPbeta, for example, by specific sandwich ELISA
10 assays. For some chronic studies, brain tissues of APP transgenic animals are also analyzed for the amount of beta-amyloid plaques following compound treatment, for example, by standard histochemical and immunohistochemical methodologies.

Animals (PDAPP or other APP transgenic or non-transgenic mice) administered an inhibitory compound may demonstrate the reduction of Abeta or sAPPbeta in brain
15 tissues, plasma or cerebrospinal fluids and decrease of beta amyloid plaques in brain tissue, as compared with vehicle-treated controls. For example, 3 hours after administration of 100 mg/kg sub-cutaneous dose of the compound of EXAMPLE 135 to young PDAPP mice, Abeta peptide levels are reduced 39%, 40% and 25% in plasma, cerebrospinal fluid and brain cortex, respectively, compared to vehicle-treated mice.
20 Animals (PDAPP or other APP transgenic mice) administered the inhibitory compounds of the invention may also show improvement in cognitive behavioral assessments for learning and memory tasks.

Oral administration of the compounds of the present invention is preferred. However, oral administration is not the only route or even the only preferred route. For
25 example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula I may also be administered by the percutaneous, intramuscular, intranasal or intrarectal route in particular circumstances. The route of administration
30 may be varied in any way, limited by the physical properties of the drugs, the

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convenience of the patient and the caregiver, and other relevant circumstances
(Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material
5 that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

10 The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the
15 present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

20 The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate, disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like;
25 lubricants such as: magnesium stearate, stearic acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate and polysorbate 80; and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the
30 above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar,

hydroxypropyl methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

5 The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above
10 dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity
15 of the patient's symptoms.

 In order to achieve or maintain appropriate levels of the compounds of Formula I in the brain of an afflicted mammal, it may be necessary or desirable to co-administer an effective amount of an inhibitor of P-glycoprotein (P-gp). P-gp inhibitors and the use of such compounds are known to those skilled in the art. (See:
20 Cancer Research, 53, 4595 (1993); Clin. Cancer Res., 2, 7 (1996); Cancer Research, 56, 4171 (1996); WO99/64001; and WO01/10387).

 The P-gp inhibitor may be administered in any manner that achieves a sufficient degree of inhibition of P-gp to achieve or maintain sufficient levels of the compounds of Formula I for effective BACE inhibition in the brain of an afflicted
25 mammal. As such, the P-gp inhibitor may be administered separately before, during, or after the administration of a compound of Formula I. Furthermore, if desirable, the P-gp inhibitor may be formulated with a compound of Formula I. These formulations and methods represent further embodiments of the present invention.

 Many suitable P-gp inhibitors are known today and undoubtedly others will be
30 identified in the future. Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10, 11-methanodibenzosuberane, phenothiazines, acridine derivatives

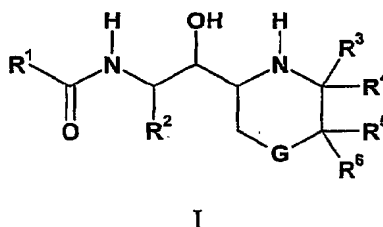
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such as GF120918, FK506, VX-710, LY355979, PSC-833, GF-102,918 and other steroids.

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We Claim:

1. A compound of Formula I:



5 where:

R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^7$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^7$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

15 R^2 is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, hydroxy, thiol, benzyloxy, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a second substituent selected from the group consisting of halo, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in

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the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is hydrogen; R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl; or a pharmaceutically acceptable salt thereof.

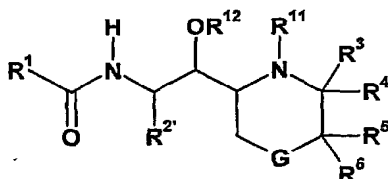
2. A pharmaceutical formulation comprising a compound of Claim 1, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

3. The use of a compound of Claim 1 for the manufacture of a medicament for the inhibition of BACE.

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4. The use of a compound of Claim 1 for the manufacture of a medicament for the treatment of Alzheimer's disease.

5. A compound of Formula II:



II

where:

R^1 is C_1 - C_{10} alkyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkenyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; C_2 - C_8 alkynyl optionally substituted with C_3 - C_8 cycloalkyl, phenyl, or furyl; or C_3 - C_8 cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C_1 - C_6 alkoxy, C_3 - C_7 cycloalkoxy, oxo, NR^7R^8 , and $C(O)NR^7R^7$; or R^1 is hydrogen; furyl optionally substituted with $C(O)NR^7R^7$ or up to two times with C_1 - C_6 alkyl; thienyl; tetrahydrofuryl; NR^7R^8 ; or C_1 - C_6 alkoxy;

$R^{2'}$ is C_1 - C_3 alkyl optionally substituted with C_3 - C_6 cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, $-OR^{12}$, thiol, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_2 - C_6 alkenyloxy, C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, C_3 - C_8 cycloalkoxy, phenyl optionally substituted with C_1 - C_6 alkyl or C_1 - C_6 alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C_3 - C_6 cycloalkyl optionally substituted with C_1 - C_3 alkyl, and a

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second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

R⁵ is R⁹; or -(CH₂)₀₋₂-OR⁹;

R⁶ is hydrogen or phenyl;

G is O;

R⁷ is selected independently at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, and phenyl;

R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);

R⁹ is hydrogen; C₁-C₁₀ alkyl optionally substituted with 1-6 fluorine atoms or tri-(C₁-C₆ alkyl)silyl; C₂-C₁₀ acyl; C₂-C₆ alkenyl; or -(CH₂)₀₋₄-R¹⁰;

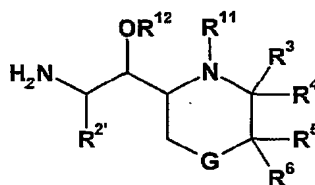
R¹⁰ is C₃-C₈ cycloalkyl; C₃-C₈ cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl; or phenyl each optionally substituted with one substituent selected from the group consisting of C₃-C₈ cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or with one or two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl;

R¹¹ is hydrogen or a nitrogen protecting group;

R¹² is hydrogen or an oxygen protecting group; or an acid addition salt thereof provided that at least one of R¹¹ and R¹² is other than hydrogen.

6. A compound of Formula III:

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III

where:

- R^{2'} is C₁-C₃ alkyl optionally substituted with C₃-C₆ cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;

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R^5 is R^9 ; or $-(CH_2)_{0-2}-OR^9$;

R^6 is hydrogen or phenyl;

G is O;

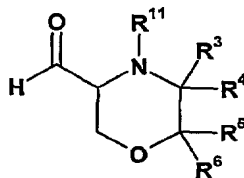
R^9 is hydrogen; C_1-C_{10} alkyl optionally substituted with 1-6 fluorine atoms or tri-
5 $(C_1-C_6 \text{ alkyl})$ silyl; C_1-C_{10} acyl; C_2-C_6 alkenyl; or $-(CH_2)_{0-4}-R^{10}$;

R^{10} is C_3-C_8 cycloalkyl; C_3-C_8 cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl;
or phenyl each optionally substituted with one substituent selected from the group
consisting of C_3-C_8 cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or one or
two substituents independently selected from the group consisting of halo, C_1-C_6 alkyl
10 optionally substituted up to three times with fluoro, C_2-C_6 acyl, C_1-C_6 alkoxy, hydroxy,
and trifluoromethoxy; or R^{10} is adamantyl;

R^{11} is hydrogen or a nitrogen protecting group;

R^{12} is hydrogen or an oxygen protecting group; or an acid addition salt thereof.

15 7. A compound of Formula IV:



IV

where:

R^3 is hydrogen or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl or up
20 to three times with fluoro and R^4 is hydrogen or C_1-C_6 alkyl; or R^3 and R^4 taken together
with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl ring;

R^5 is R^9 ; or $-(CH_2)_{0-2}-OR^9$;

R^6 is hydrogen or phenyl;

R^9 is hydrogen; C_1-C_{10} alkyl optionally substituted with 1-6 fluorine atoms or tri-
25 $(C_1-C_6 \text{ alkyl})$ silyl; C_1-C_{10} acyl; C_2-C_6 alkenyl; or $-(CH_2)_{0-4}-R^{10}$;

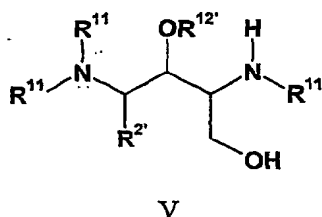
R^{10} is C_3-C_8 cycloalkyl; C_3-C_8 cycloalkanonyl; tetrahydrofuryl; tetrahydropyranyl;
or phenyl each optionally substituted with one substituent selected from the group
consisting of C_3-C_8 cycloalkyl, phenyl, and benzyl, up to four times with fluoro, or one or

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two substituents independently selected from the group consisting of halo, C₁-C₆ alkyl optionally substituted up to three times with fluoro, C₂-C₆ acyl, C₁-C₆ alkoxy, hydroxy, and trifluoromethoxy; or R¹⁰ is adamantyl;

R¹¹ is a nitrogen protecting group; provided that at least one of R³, R⁴, R⁵, and R⁶ are other than hydrogen.

8. A compound of Formula V:



10 where:

R^{2'} is C₁-C₃ alkyl optionally substituted with C₃-C₆ cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆

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alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;

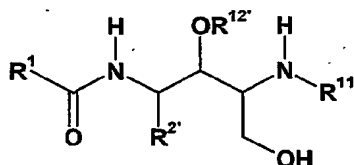
R¹¹ is independently at each instance a nitrogen protecting group;

5 R^{11'} is hydrogen or a nitrogen protecting group;

R¹² is hydrogen or an oxygen protecting group;

R^{12'} is an oxygen protecting group; or an acid addition salt thereof.

9. A compound of Formula VI:



VI

where:

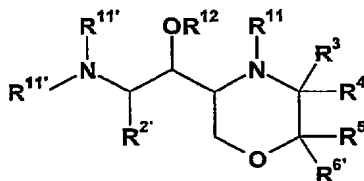
R¹ is C₁-C₁₀ alkyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl; C₂-C₈ alkenyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl; C₂-C₈ alkynyl optionally substituted with C₃-C₈ cycloalkyl, phenyl, or furyl; or C₃-C₈ cycloalkyl; each optionally substituted up to six times with fluoro, or with up to four substituents independently selected from the group consisting of halo, cyano, methyl optionally substituted with up to three fluoro atoms, trifluoromethoxy, C₁-C₆ alkoxy, C₃-C₇ cycloalkoxy, oxo, NR⁷R⁸, and C(O)NR⁷R⁷; or R¹ is hydrogen; furyl optionally substituted with C(O)NR⁷R⁷ or up to two times with C₁-C₆ alkyl; thienyl; tetrahydrofuryl; NR⁷R⁸; or C₁-C₆ alkoxy;

R^{2'} is C₁-C₃ alkyl optionally substituted with C₃-C₆ cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally

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- substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a
- 5 second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in
- 10 the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;
- 15 R⁷ is selected independently at each occurrence from the group consisting of hydrogen; C₁-C₆ alkyl; and phenyl;
- R⁸ is hydrogen; C₁-C₆ alkyl; phenyl; -C(O)(C₁-C₆ alkyl); or -SO₂(C₁-C₆ alkyl);
- R^{11'} is hydrogen or a nitrogen protecting group;
- R¹² is hydrogen or an oxygen protecting group;
- 20 R^{12'} is an oxygen protecting group; or an acid addition salt thereof.

10. A compound of Formula VII:



VII

25 where:

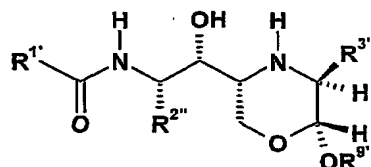
R^{2'} is C₁-C₃ alkyl optionally substituted with C₃-C₆ cycloalkyl; benzyl optionally monosubstituted in the phenyl ring with a substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to

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- three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo, trifluoromethoxy, and C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, and a second substituent selected from the group consisting of halo, -OR¹², thiol, C₁-C₆ alkyl optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₁-C₆ alkoxy optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl, C₂-C₆ alkenyloxy, C₁-C₆ alkylthio optionally substituted in the alkyl chain up to three times with fluoro or with C₃-C₆ cycloalkyl optionally substituted with C₁-C₃ alkyl C₃-C₈ cycloalkoxy, phenyl optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy, and phenylthio; or benzyl trisubstituted in the phenyl ring with three substituents independently selected from halo or two substituents independently selected from halo and a third substituent selected from C₁-C₆ alkyl;
- R³ is hydrogen or C₁-C₆ alkyl optionally substituted with C₃-C₈ cycloalkyl or up to three times with fluoro and R⁴ is hydrogen or C₁-C₆ alkyl; or R³ and R⁴ taken together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl ring;
- R^{5'} is hydroxy and R^{6'} is hydrogen or R^{5'} and R^{6'} together with the carbon to which they are attached form a carbonyl moiety;
- R¹¹ is a nitrogen protecting group;
- R^{11'} is hydrogen or a nitrogen protecting group;
- R¹² is hydrogen or an oxygen protecting group; or an acid addition salt thereof.

11. A compound of Formula I(a):

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I(a)

where;

5 $R^{1'}$ is hydrogen; benzyl; or C_1 - C_8 alkyl optionally substituted with C_1 - C_6 alkoxy, oxo, or up to six times with fluoro;

10 $R^{2''}$ is benzyl optionally monosubstituted in the 3-position of the phenyl ring with a substituent selected from the group consisting of halo, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro, and C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro; or benzyl disubstituted in the phenyl ring with a first substituent selected from the group consisting of halo and trifluoromethoxy and a second substituent selected from the group consisting of halo, C_1 - C_6 alkyl optionally substituted in the alkyl chain up to three times with fluoro, C_1 - C_6 alkoxy optionally substituted in the alkyl chain up to three times with fluoro, or C_1 - C_6 alkylthio optionally substituted in the alkyl chain up to three times with fluoro;

$R^{3'}$ is hydrogen or C_1 - C_4 alkyl;

$R^{9'}$ is C_1 - C_{10} alkyl optionally substituted with 1-6 fluorine atoms; C_1 - C_4 alkyl substituted with tetrahydrofuryl, tetrahydropyranyl, or C_3 - C_8 cycloalkyl optionally substituted with up to 4 fluoro atoms; or a pharmaceutically acceptable salt thereof.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034093 A3

(51) International Patent Classification:

C07D 265/30 (2006.01) C07D 413/12 (2006.01)
C07D 265/32 (2006.01) C07C 217/48 (2006.01)
A61K 31/5375 (2006.01) C07C 271/20 (2006.01)
A61K 31/5377 (2006.01) C07F 7/18 (2006.01)

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(21) International Application Number:

PCT/US2005/033277

(22) International Filing Date:

20 September 2005 (20.09.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/611,718 21 September 2004 (21.09.2004) US
60/696,949 6 July 2005 (06.07.2005) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY,
MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

- with international search report

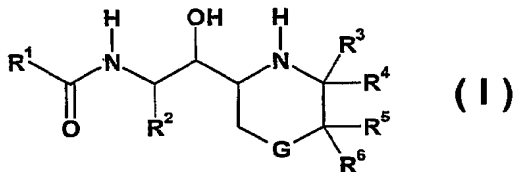
(88) Date of publication of the international search report:

13 July 2006

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 2006/034093 A3

(54) Title: 3- (2-ACYLAMINO-1-HYDROXYETHYL)- MORPHOLINE DERIVATIVES AND THEIR USE AS BACE
INHIBITORS



(57) Abstract: The present invention provides BACE
inhibitors of Formula (I); methods for their use and
preparation, and intermediates useful for their preparation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/033277

| A. CLASSIFICATION OF SUBJECT MATTER INV. C07D265/30 C07D265/32 A61K31/5375 A61K31/5377 C07D413/12 C07C217/48 C07C271/20 C07F7/18 | | |
|---|---|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D C07C C07F Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | WO 2004/043916 A (MERCK & CO., INC; COBURN, CRAIG, A; STACHEL, SHAWN, J; VACCA, JOSEPH,) 27 May 2004 (2004-05-27) the whole document | 1-11 |
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| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. | | |
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| Date of the actual completion of the international search | | Date of mailing of the international search report |
| 14 March 2006 | | 27/03/2006 |
| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer Fink, D |

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/033277

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Information on patent family members

International application No

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